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(71) Applicant *(for all designated States except US)*: **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **FRALEY, Mark, E.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **HOFFMAN, William, F.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

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(54) Title: MITOTIC KINESIN INHIBITORS

(57) Abstract: The present invention relates to quinazolinone compounds that are useful for treating cellular proliferative diseases, for treating disorders associated with KSP kinesin activity, and for inhibiting KSP kinesin. The invention also related to compositions which comprise these compounds, and methods of using them to treat cancer in mammals.

TITLE OF THE INVENTION

MITOTIC KINESIN INHIBITORS

BACKGROUND OF THE INVENTION

This invention relates to quinazolinone derivatives that are inhibitors of mitotic kinesins, in particular the mitotic kinesin KSP, and are useful in the treatment of cellular proliferative diseases, for example cancer, hyperplasias, restenosis, cardiac hypertrophy, immune disorders and inflammation.

Quinazolinones and derivatives thereof are known to have a Wide variety of biological properties including hypnotic, sedative, analgesic, anticonvulsant, antitussive and anti-inflammatory activities.

Quinazolinone derivatives for which specific biological uses have been described include U.S. Patent No. 5,147,875 describing 2-(substituted phenyl)-4-oxo quinazolines with bronchodilator activity; U.S. Patent Nos. 3,723,432, 3,740,442, and 3,925,548 describe a class of I -substituted-4-aryl-2(l H)-quinazolinone derivatives useful as anti-inflammatory agents; European patent publication EP 0 056 637 B1 claims a class of 4(3H)-quinazolinone derivatives for the treatment of hypertension; and European patent publication EP 0 884 319 Al describes pharmaceutical compositions of quinazolin-4-one derivatives used to treat neurodegenerative, psychotropic, and drug and alcohol induced central and peripheral nervous system disorders.

Quinazolinones are among a growing number of therapeutic agents used to treat cell proliferative disorders, including cancer. For example, PCT WO 96/06616 describes a pharmaceutical composition containing a quinazolinone derivative to inhibit vascular smooth cell proliferation. PCT WO 96/19224 uses this same quinazolinone derivative to inhibit mesengial cell proliferation. U.S. Patent Nos. 4,981,856, 5,081,124 and 5,280,027 describe the use of quinazolinone derivatives to inhibit thymidylate synthase, the enzyme that catalyzes the methylation of deoxyuridine monophosphate to produce thymidine monophosphate which is required for DNA synthesis. U.S. Patent Nos. 5,747,498 and 5,773,476 describe quinazolinone derivatives used to treat cancers characterized by over-activity or inappropriate activity of tyrosine receptor kinases. U.S. Patent No. 5,037,829 claims (IH-azol-1-ylmethyl) substituted quinazoline compositions to treat carcinomas that occur in epithelial cells. PCT WO 98/34613 describes a composition containing a

quinazolinone derivative useful for attenuating neovascularization and for treating malignancies. U.S. Patent 5,187,167 describes pharmaceutical compositions comprising quinazolin-4-one derivatives that possess anti-tumor activity.

Other therapeutic agents used to treat cancer include the taxanes and vinca alkaloids. Taxanes and vinca alkaloids act on microtubules, which are present in a variety of cellular structures. Microtubules are the primary structural element of the mitotic spindle. The mitotic spindle is responsible for distribution of replicate copies of the genome to each of the two daughter cells that result from cell division. It is presumed that disruption of the mitotic spindle by these drugs results in inhibition of cancer cell division, and induction of cancer cell death. However, microtubules form other types of cellular structures, including tracks for intracellular transport in nerve processes. Because these agents do not specifically target mitotic spindles, they have side effects that limit their usefulness.

Improvements in the specificity of agents used to treat cancer is of considerable interest because of the therapeutic benefits which would be realized if the side effects associated with the administration of these agents could be reduced. Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms. Examples of this include not only the taxanes, but also the camptothecin class of topoisomerase I inhibitors. From both of these perspectives, mitotic kinesins are attractive targets for new anti-cancer agents.

Mitotic kinesins are enzymes essential for assembly and function of the mitotic spindle, but are not generally part of other microtubule structures, such as in nerve processes. Mitotic kinesins play essential roles during all phases of mitosis. These enzymes are "molecular motors" that transform energy released by hydrolysis of ATP into 'mechanical force which drives the directional movement of cellular cargoes along microtubules. The catalytic domain sufficient for this task is a compact structure of approximately 340 amino acids. During mitosis, kinesins organize microtubules into the bipolar structure that is the mitotic spindle. Kinesins mediate movement of chromosomes along spindle microtubules, as well as structural changes in the mitotic spindle associated with specific phases of mitosis. Experimental perturbation of mitotic kinesin function causes malformation or dysfunction of the mitotic spindle, frequently resulting in cell cycle arrest and cell death.

Among the mitotic kinesins which have been identified is KSP. KSP belongs to an evolutionarily conserved kinesin subfamily of plus end-directed microtubule motors that assemble into bipolar homotetramers consisting of antiparallel homodimers. During mitosis KSP associates with microtubules of the mitotic spindle. Microinjection of antibodies directed against KSP into human cells prevents spindle pole separation during prometaphase, giving rise to monopolar spindles and causing mitotic arrest and induction of programmed cell death. KSP and related kinesins in other, non-human, organisms, bundle antiparallel microtubules and slide them relative to one another, thus forcing the two spindle poles apart. KSP may also mediate in anaphase B spindle elongation and focussing of microtubules at the spindle pole.

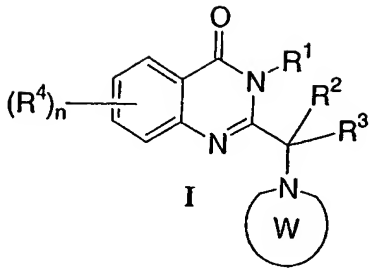
Human KSP (also termed HsEg5) has been described [Blangy, et al., Cell, 83:1159-69 (1995); Whitehead, et al., Arthritis Rheum., 39:1635-42 (1996); Galgio et al., J. Cell Biol., 135:339-414 (1996); Blangy, et al., J Biol. Chem., 272:19418-24 (1997); Blangy, et al., Cell Motil Cytoskeleton, 40:174-82 (1998); Whitehead and Rattner, J. Cell Sci., 111:2551-61 (1998); Kaiser, et al., JBC 274:18925-31 (1999); GenBank accession numbers: X85137, NM004523 and U37426] , and a fragment of the KSP gene (TRIP5) has been described [Lee, et al., Mol Endocrinol., 9:243-54 (1995); GenBank accession number L40372]. Xenopus KSP homologs (Eg5), as well as Drosophila K-LP61 F/KRP 130 have been reported.

Certain quinazolinones have recently been described as being inhibitors of KSP (PCT Publ. WO 01/30768, May 3, 2001).

Mitotic kinesins are attractive targets for the discovery and development of novel mitotic chemotherapeutics. Accordingly, it is an object of the present invention to provide compounds, methods and compositions useful in the inhibition
of KSP, a mitotic kinesin.

SUMMARY OF THE INVENTION

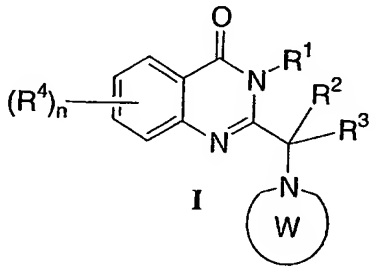
The present invention relates to quinazolinone compounds that are useful for treating cellular proliferative diseases, for treating disorders associated with KSP kinesin activity, and for inhibiting KSP kinesin. The compounds of the invention may be illustrated by the Formula I:



I

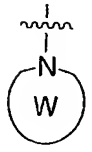
DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the inhibition of mitotic kinesins and are illustrated by a compound of Formula I:



I

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein



is a 5-12 membered nitrogen-containing heterocycle, which is optionally substituted with from one to six R^5 groups and which optionally incoporates from one to two additional heteroatoms, selected from N, O and S in the heterocycle ring;

a is 0 or 1;
b is 0 or 1;
m is 0, 1, or 2;
n is 0 to 4;

R^1 is selected from:

1) H,
2) C_1-C_{10} alkyl,

3) aryl,
4) C_2-C_{10} alkenyl,
5) C_2-C_{10} alkynyl,
6) C_1-C_6 perfluoroalkyl,
7) C_3-C_8 cycloalkyl, and
8) heterocyclyl,

said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R^5;

R^2 and R^3 are independently selected from:
1) H,
2) $(C=O)_aO_bC_1$-C_{10} alkyl,
3) $(C=O)_aO_b$aryl,
4) $(C=O)_aO_bC_2$-C_{10} alkenyl,
5) $(C=O)_aO_bC_2$-C_{10} alkynyl,
6) CO_2H,
7) C_1-C_6 perfluoroalkyl,
8) $(C=O)_aO_bC_3$-C_8 cycloalkyl,
9) $(C=O)_aO_b$heterocyclyl,
10) $SO_2NR^7R^8$, and
11) SO_2C_1-C_{10} alkyl,

said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R^5;

R^4 is independently selected from:
1) $(C=O)_aO_bC_1$-C_{10} alkyl,
2) $(C=O)_aO_b$aryl,
3) $(C=O)_aO_bC_2$-C_{10} alkenyl,
4) $(C=O)_aO_bC_2$-C_{10} alkynyl,
5) CO_2H,
6) halo,
7) OH,
8) O_bC_1-C_6 perfluoroalkyl,
9) $(C=O)_aNR^7R^8$,

10) CN,
11) $(C=O)_aO_bC_3$-C_8 cycloalkyl,
12) $(C=O)_aO_b$heterocyclyl,
13) $SO_2NR^7R^8$, and
14) SO_2C_1-C_{10} alkyl,

said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R^5;

R^5 is:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,
2) $(C=O)_aO_b$aryl,
3) C_2-C_{10} alkenyl,
4) C_2-C_{10} alkynyl,
5) $(C=O)_aO_b$ heterocyclyl,
6) CO_2H,
7) halo,
8) CN,
9) OH,
10) O_bC_1-C_6 perfluoroalkyl,
11) $O_a(C=O)_bNR^7R^8$,
12) oxo,
13) CHO,
14) $(N=O)R^7R^8$, or
15) $(C=O)_aO_bC_3$-C_8 cycloalkyl,

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from R^6;

R^6 is selected from:

1) $(C=O)_rO_s(C_1$-$C_{10})$alkyl, wherein r and s are independently 0 or 1,
2) $O_r(C_1$-$C_3)$perfluoroalkyl, wherein r is 0 or 1,
3) $(C_0$-$C_6)$alkylene-$S(O)_mR^a$, wherein m is 0, 1, or 2,
4) oxo,
5) OH,
6) halo,

7) CN,
8) $(C=O)_rO_s(C_2\text{-}C_{10})$alkenyl,
9) $(C=O)_rO_s(C_2\text{-}C_{10})$alkynyl,
10) $(C=O)_rO_s(C_3\text{-}C_6)$cycloalkyl,
11) $(C=O)_rO_s(C_0\text{-}C_6)$alkylene-aryl,
12) $(C=O)_rO_s(C_0\text{-}C_6)$alkylene-heterocyclyl,
13) $(C=O)_rO_s(C_0\text{-}C_6)$alkylene-$N(R^b)_2$,
14) $C(O)R^a$,
15) $(C_0\text{-}C_6)$alkylene-CO_2R^a,
16) C(O)H,
17) $(C_0\text{-}C_6)$alkylene-CO_2H, and
18) $C(O)N(R^b)_2$,

said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from R^b, OH, $(C_1\text{-}C_6)$alkoxy, halogen, CO_2H, CN, $O(C=O)C_1\text{-}C_6$ alkyl, oxo, and $N(R^b)_2$;

R^7 and R^8 are independently selected from:

1) H,
2) $(C=O)O_bC_1\text{-}C_{10}$ alkyl,
3) $(C=O)O_bC_3\text{-}C_8$ cycloalkyl,
4) $(C=O)O_b$aryl,
5) $(C=O)O_b$heterocyclyl,
6) $C_1\text{-}C_{10}$ alkyl,
7) aryl,
8) $C_2\text{-}C_{10}$ alkenyl,
9) $C_2\text{-}C_{10}$ alkynyl,
10) heterocyclyl,
11) $C_3\text{-}C_8$ cycloalkyl,
12) SO_2R^a, and
13) $(C=O)NR^b{}_2$,

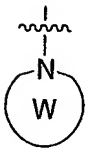
said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from R^6, or

R^7 and R^8 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocylcic or bicyclic heterocycle optionally substituted with one or more substituents selected from R^6;

R^a is $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, aryl, or heterocyclyl; and

R^b is H, $(C_1\text{-}C_6)$alkyl, aryl, heterocyclyl, $(C_3\text{-}C_6)$cycloalkyl, $(C{=}O)OC_1\text{-}C_6$ alkyl, $(C{=}O)C_1\text{-}C_6$ alkyl or $S(O)_2R^a$.

A second embodiment of the invention is a compound of Formula I, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein



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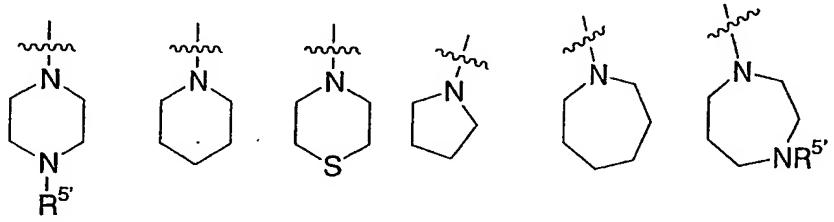


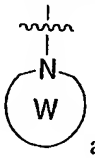
optionally substituted with from one to three R^5 groups; and

$R^{5'}$ is:

1) H,
2) $C_1\text{-}C_{10}$ alkyl,
3) aryl,
4) $C_2\text{-}C_{10}$ alkenyl,
5) $C_2\text{-}C_{10}$ alkynyl,
6) heterocyclyl,
7) OH,

8) C_1-C_6 perfluoroalkyl,
9) C_3-C_8 cycloalkyl;

said alkyl, aryl, alkenyl, alkynyl and heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from R^6.

A further embodiment of the present invention is illustrated by a compound of Formula I, or a pharmaceutically acceptable salt or stereoisomer thereof, with  as defined immediately above, wherein

a is 0 or 1;
b is 0 or 1;
m is 0, 1, or 2;
n is 0 to 4;

R^1 is selected from:

1) H,
2) C_1-C_{10} alkyl,
3) aryl,
4) C_3-C_8 cycloalkyl, and
5) heterocyclyl,

said alkyl, aryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R^5;

R^2 and R^3 are independently selected from:

1) H,
2) $(C=O)_aO_bC_1$-C_{10} alkyl,
3) $(C=O)_aO_b$aryl,
4) CO_2H,
5) C_1-C_6 perfluoroalkyl,
6) $(C=O)_aO_bC_3$-C_8 cycloalkyl, and
7) $(C=O)_aO_b$heterocyclyl,

said alkyl, aryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R^5;

R^4 is independently selected from:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,
2) $(C=O)_aO_b$aryl,
3) CO_2H,
4) halo,
5) OH,
6) O_bC_1-C_6 perfluoroalkyl,
7) $(C=O)_aNR^7R^8$,
8) CN,
9) $(C=O)_aO_b$heterocyclyl,
10) $SO_2NR^7R^8$, and
11) SO_2C_1-C_{10} alkyl,

said alkyl, aryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R^5;

R^5 is:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,
2) $(C=O)_aO_b$aryl,
3) C_2-C_{10} alkenyl,
4) C_2-C_{10} alkynyl,
5) $(C=O)_aO_b$ heterocyclyl,
6) CO_2H,
7) halo,
8) CN,
9) OH,
10) O_bC_1-C_6 perfluoroalkyl,
11) $O_a(C=O)_bNR^7R^8$,
12) oxo,
13) CHO,
14) $(N=O)R^7R^8$, or
15) $(C=O)_aO_bC_3$-C_8 cycloalkyl,

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from R^6;

$R^{5'}$ is:

1) H,
2) C_1-C_{10} alkyl,
3) aryl,
4) C_2-C_{10} alkenyl,
5) C_2-C_{10} alkynyl,
6) heterocyclyl,
7) OH,
8) C_1-C_6 perfluoroalkyl,
9) C_3-C_8 cycloalkyl;

said alkyl, aryl, alkenyl, alkynyl and heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from R^6;

R^6 is selected from:

1) $(C=O)_rO_s(C_1$-$C_{10})$alkyl, wherein r and s are independently 0 or 1,
2) $O_r(C_1$-$C_3)$perfluoroalkyl, wherein r is 0 or 1,
3) oxo,
4) OH,
5) halo,
6) CN,
7) $(C_2$-$C_{10})$alkenyl,
8) $(C_2$-$C_{10})$alkynyl,
9) $(C=O)_rO_s(C_3$-$C_6)$cycloalkyl,
10) $(C=O)_rO_s(C_0$-$C_6)$alkylene-aryl,
11) $(C=O)_rO_s(C_0$-$C_6)$alkylene-heterocyclyl,
12) $(C=O)_rO_s(C_0$-$C_6)$alkylene-$N(R^b)_2$,
13) $C(O)R^a$,
14) $(C_0$-$C_6)$alkylene-CO_2R^a,
15) C(O)H,
16) $(C_0$-$C_6)$alkylene-CO_2H, and
17) $C(O)N(R^b)_2$,

said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from R^b, OH, $(C_1\text{-}C_6)$alkoxy, halogen, CO_2H, CN, $O(C=O)C_1\text{-}C_6$ alkyl, oxo, and $N(R^b)_2$;

R^7 and R^8 are independently selected from:

1) H,
2) $(C=O)O_bC_1\text{-}C_{10}$ alkyl,
3) $(C=O)O_bC_3\text{-}C_8$ cycloalkyl,
4) $(C=O)O_b$aryl,
5) $(C=O)O_b$heterocyclyl,
6) $C_1\text{-}C_{10}$ alkyl,
7) aryl,
8) $C_2\text{-}C_{10}$ alkenyl,
9) $C_2\text{-}C_{10}$ alkynyl,
10) heterocyclyl,
11) $C_3\text{-}C_8$ cycloalkyl,
12) SO_2R^a, and
13) $(C=O)NR^b{}_2$,

said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from R^6, or

R^7 and R^8 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocylcic or bicyclic heterocycle optionally substituted with one or more substituents selected from R^6;

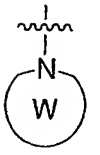
R^a is $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, aryl, or heterocyclyl; and

R^b is H, $(C_1\text{-}C_6)$alkyl, aryl, heterocyclyl, $(C_3\text{-}C_6)$cycloalkyl, $(C=O)OC_1\text{-}C_6$ alkyl, $(C=O)C_1\text{-}C_6$ alkyl or $S(O)_2R^a$.

Another embodiment is the compound described immediately above, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^3 is defined as H.

And yet another embodiment is wherein R^1 is selected from: (C_1-C_6)alkyl, aryl and benzyl.

Another embodiment of the present invention is illustrated by a compound of Formula I, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein



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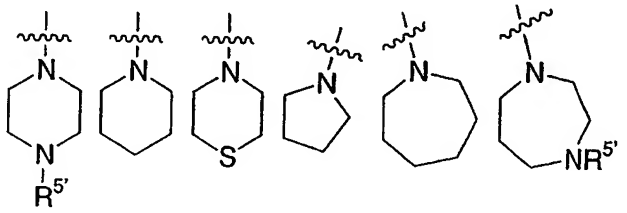


optionally substituted with from one to three R^5 groups;

a is 0 or 1;
b is 0 or 1;
m is 0, 1, or 2;
n is 0 to 4;

R^1 is benzyl, optionally substituted with one to three substituents selected from R^5;

R^2 is C_2-C_6 alkyl;

R^3 is H;

R^4 is independently selected from:

1) $(C{=}O)_aO_bC_1$-C_{10} alkyl,
2) $(C{=}O)_aO_b$aryl,
3) CO_2H,
4) halo,
5) OH,
6) O_bC_1-C_6 perfluoroalkyl,

7) $(C=O)_aNR^7R^8$,
8) CN,
9) $(C=O)_aO_b$heterocyclyl,
10) $SO_2NR^7R^8$, and
11) SO_2C_1-C_{10} alkyl,

said alkyl, aryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R^5;

R^5 is:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,
2) $(C=O)_aO_b$aryl,
3) C_2-C_{10} alkenyl,
4) C_2-C_{10} alkynyl,
5) $(C=O)_aO_b$ heterocyclyl,
6) CO_2H,
7) halo,
8) CN,
9) OH,
10) O_bC_1-C_6 perfluoroalkyl,
11) $O_a(C=O)_bNR^7R^8$,
12) oxo,
13) CHO,
14) $(N=O)R^7R^8$, or
15) $(C=O)_aO_bC_3$-C_8 cycloalkyl,

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from R^6;

$R^{5'}$ is:

1) H,
2) C_1-C_{10} alkyl,
3) aryl,
4) C_2-C_{10} alkenyl,
5) C_2-C_{10} alkynyl,
6) heterocyclyl,

7) OH,
8) C_1-C_6 perfluoroalkyl,
9) C_3-C_8 cycloalkyl;

said alkyl, aryl, alkenyl, alkynyl and heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from R^6;

R^6 is selected from:

1) $(C=O)_rO_s(C_1$-$C_{10})$alkyl, wherein r and s are independently 0 or 1,
2) $O_r(C_1$-$C_3)$perfluoroalkyl, wherein r is 0 or 1,
3) oxo,
4) OH,
5) halo,
6) CN,
7) $(C_2$-$C_{10})$alkenyl,
8) $(C_2$-$C_{10})$alkynyl,
9) $(C=O)_rO_s(C_3$-$C_6)$cycloalkyl,
10) $(C=O)_rO_s(C_0$-$C_6)$alkylene-aryl,
11) $(C=O)_rO_s(C_0$-$C_6)$alkylene-heterocyclyl,
12) $(C=O)_rO_s(C_0$-$C_6)$alkylene-$N(R^b)_2$,
13) $C(O)R^a$,
14) $(C_0$-$C_6)$alkylene-CO_2R^a,
15) C(O)H,
16) $(C_0$-$C_6)$alkylene-CO_2H, and
17) $C(O)N(R^b)_2$,

said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from R^b, OH, $(C_1$-$C_6)$alkoxy, halogen, CO_2H, CN, $O(C=O)C_1$-C_6 alkyl, oxo, and $N(R^b)_2$;

R^7 and R^8 are independently selected from:

1) H,
2) $(C=O)O_bC_1$-C_{10} alkyl,
3) $(C=O)O_bC_3$-C_8 cycloalkyl,
4) $(C=O)O_b$aryl,
5) $(C=O)O_b$heterocyclyl,

6) C_1-C_{10} alkyl,
7) aryl,
8) C_2-C_{10} alkenyl,
9) C_2-C_{10} alkynyl,
10) heterocyclyl,
11) C_3-C_8 cycloalkyl,
12) SO_2R^a, and
13) $(C=O)NR^b{}_2$,

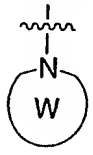
said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from R^6, or

R^7 and R^8 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocyclic or bicyclic heterocycle optionally substituted with one or more substituents selected from R^6;

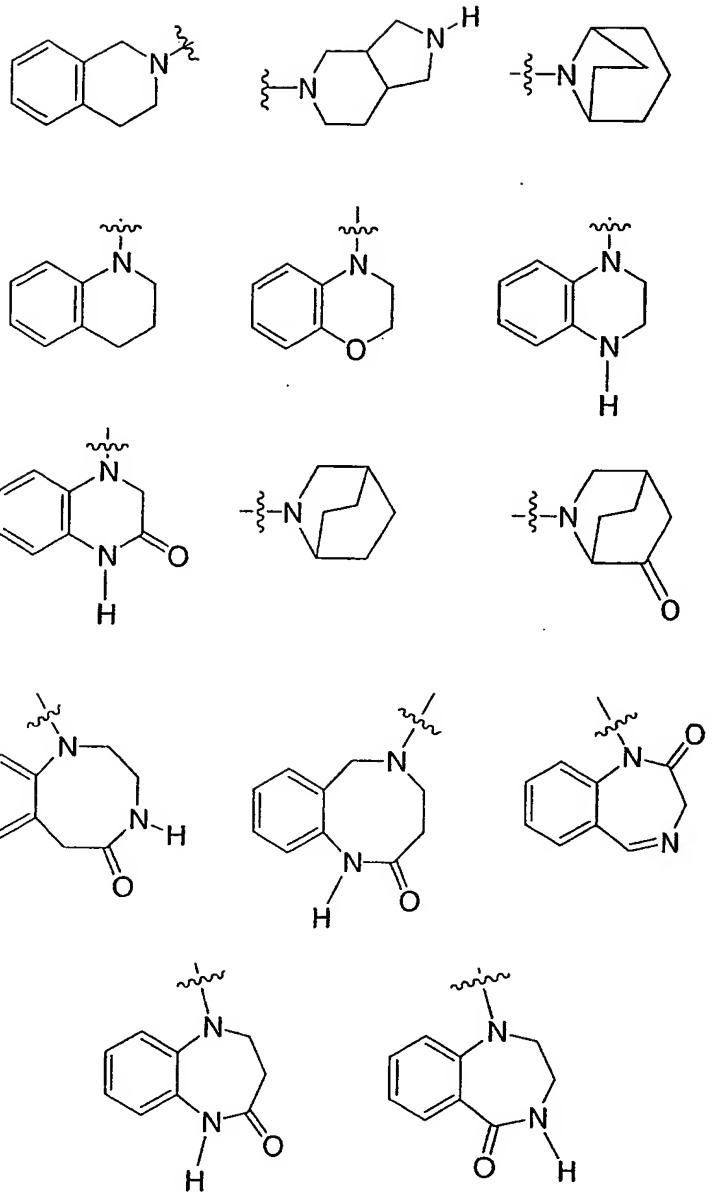
R^a is $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, aryl, or heterocyclyl; and

R^b is H, $(C_1$-$C_6)$alkyl, aryl, heterocyclyl, $(C_3$-$C_6)$cycloalkyl, $(C=O)OC_1$-C_6 alkyl, $(C=O)C_1$-C_6 alkyl or $S(O)_2R^a$.

Another embodiment of the present invention is illustrated by a compound of Formula I, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein



is selected from:



optionally substituted with from one to three R^5 groups;

a is 0 or 1;

b is 0 or 1;

m is 0, 1, or 2;

n is 0 to 4;

R^1 is benzyl, optionally substituted with one to three substituents selected from R^5;

R^2 is C_2-C_6 alkyl;

R^3 is H;

R^4 is independently selected from:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,
2) $(C=O)_aO_b$aryl,
3) CO_2H,
4) halo,
5) OH,
6) O_bC_1-C_6 perfluoroalkyl,
7) $(C=O)_aNR^7R^8$,
8) CN,
9) $(C=O)_aO_b$heterocyclyl,
10) $SO_2NR^7R^8$, and
11) SO_2C_1-C_{10} alkyl,

said alkyl, aryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R^5;

R^5 is:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,
2) $(C=O)_aO_b$aryl,
3) C_2-C_{10} alkenyl,
4) C_2-C_{10} alkynyl,
5) $(C=O)_aO_b$ heterocyclyl,
6) CO_2H,
7) halo,
8) CN,
9) OH,
10) O_bC_1-C_6 perfluoroalkyl,

11) $O_a(C=O)_bNR^7R^8$,
12) oxo,
13) CHO,
14) $(N=O)R^7R^8$, or
15) $(C=O)_aO_bC_3$-C_8 cycloalkyl,

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from R^6;

R^6 is selected from:

1) $(C=O)_rO_s(C_1$-$C_{10})$alkyl, wherein r and s are independently 0 or 1,
2) $O_r(C_1$-$C_3)$perfluoroalkyl, wherein r is 0 or 1,
3) oxo,
4) OH,
5) halo,
6) CN,
7) $(C_2$-$C_{10})$alkenyl,
8) $(C_2$-$C_{10})$alkynyl,
9) $(C=O)_rO_s(C_3$-$C_6)$cycloalkyl,
10) $(C=O)_rO_s(C_0$-$C_6)$alkylene-aryl,
11) $(C=O)_rO_s(C_0$-$C_6)$alkylene-heterocyclyl,
12) $(C=O)_rO_s(C_0$-$C_6)$alkylene-$N(R^b)_2$,
13) $C(O)R^a$,
14) $(C_0$-$C_6)$alkylene-CO_2R^a,
15) C(O)H,
16) $(C_0$-$C_6)$alkylene-CO_2H, and
17) $C(O)N(R^b)_2$,

said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from R^b, OH, $(C_1$-$C_6)$alkoxy, halogen, CO_2H, CN, $O(C=O)C_1$-C_6 alkyl, oxo, and $N(R^b)_2$;

R^7 and R^8 are independently selected from:

1) H,
2) $(C=O)O_bC_1$-C_{10} alkyl,
3) $(C=O)O_bC_3$-C_8 cycloalkyl,

4) $(C=O)O_b$aryl,
5) $(C=O)O_b$heterocyclyl,
6) C_1-C_{10} alkyl,
7) aryl,
8) C_2-C_{10} alkenyl,
9) C_2-C_{10} alkynyl,
10) heterocyclyl,
11) C_3-C_8 cycloalkyl,
12) SO_2R^a, and
13) $(C=O)NR^b{}_2$,

said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from R^6, or

R^7 and R^8 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocylcic or bicyclic heterocycle optionally substituted with one or more substituents selected from R^6;

R^a is $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, aryl, or heterocyclyl; and

R^b is H, $(C_1$-$C_6)$alkyl, aryl, heterocyclyl, $(C_3$-$C_6)$cycloalkyl, $(C=O)OC_1$-C_6 alkyl, $(C=O)C_1$-C_6 alkyl or $S(O)_2R^a$.

Specific example of the compounds of the instant invention include:

3-benzyl-2-[1-(4-methylpiperazin-1-yl)propyl]quinazolin-4(3H)-one;

3-benzyl-2-{1-[4-(2-hydroxyethyl)piperazin-1-yl]propyl}quinazolin-4(3H)-one;

3-benzyl-2-(1-{4-[2-(2-hydroxyethoxy)ethyl]-piperazin-1-yl}propyl)quinazolin-4(3H)-one;

3-benzyl-2-[1-(4-benzylpiperazin-1-yl)propyl]quinazolin-4(3H)-one;

3-benzyl-2-{1-[4-(2-morpholin-4-yl-2-oxoethyl)piperazin-1-yl]propyl}quinazolin-4(3H)-one;

3-benzyl-2-{1-[4-(2-oxo-2-pyrrolidin-1-ylethyl)piperazin-1-yl]propyl}quinazolin-4(3H)-one;

3-benzyl-2-{1-[4-(pyridin-2-ylmethyl)piperazin-1-yl]propyl}quinazolin-4(3H)-one;

3-benzyl-2-(1-{3-[(dimethylamino)methyl]-piperidin-1-yl}propyl)quinazolin-4(3H)-one;

3-benzyl-2-(1-piperazin-1-ylpropyl)quinazolin-4(3H)-one;

3-benzyl-2-[1-(2,5-dimethylpiperazin-1-yl)propyl]quinazolin-4(3H)-one;

4-[1-(3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl]piperazine-2-carboxamide;

and the pharmaceutically acceptable salts and optical isomers thereof.

A preferred embodiment is a compound selected from

3-benzyl-2-[1-(4-methylpiperazin-1-yl)propyl]quinazolin-4(3H)-one;

3-benzyl-2-{1-[4-(2-hydroxyethyl)piperazin-1-yl]propyl}quinazolin-4(3H)-one;

3-benzyl-2-[1-(4-benzylpiperazin-1-yl)propyl]quinazolin-4(3H)-one;

3-benzyl-2-{1-[4-(2-morpholin-4-yl-2-oxoethyl)piperazin-1-yl]propyl}quinazolin-4(3H)-one;

3-benzyl-2-(1-{3-[(dimethylamino)methyl]-piperidin-1-yl}propyl)quinazolin-4(3H)-one;

or a pharmaceutically acceptable salt or stereoisomer thereof.

The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in: E.L. Eliel and S.H. Wilen, *Stereochemistry of Carbon Compounds*, John Wiley & Sons, New York, 1994, pages 1119-1190), and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers and mixtures thereof, including optical isomers, being included in the present invention. In addition, the compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted. For example, any claim to compound A below is understood to include tautomeric structure B, and vice versa, as well as mixtures thereof.

A B

When any variable (e.g. R^4, R^5, R^6, etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds. Lines drawn into the ring systems from substituents indicate that the indicated bond may be attached to any of the substitutable ring atoms. If the ring system is polycyclic, it is intended that the bond be attached to any of the suitable carbon atoms on the proximal ring only.

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results. The phrase "optionally substituted with one or more substituents" should be taken to be equivalent to the phrase "optionally substituted with at least one substituent" and in such cases the preferred embodiment will have from zero to three substituents.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, C_1-C_{10}, as in "C_1-C_{10} alkyl" is defined to include groups having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbons in a linear or branched arrangement. For example, "C_1-C_{10} alkyl" specifically includes methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *i*-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, and so on. The term "cycloalkyl" means a monocyclic saturated aliphatic hydrocarbon group having the specified number of carbon atoms. For example, "cycloalkyl" includes cyclopropyl, methyl-cyclopropyl, 2,2-dimethyl-cyclobutyl, 2-ethyl-cyclopentyl, cyclohexyl, and so on.

"Alkoxy" represents either a cyclic or non-cyclic alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Alkoxy" therefore encompasses the definitions of alkyl and cycloalkyl above.

If no number of carbon atoms is specified, the term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four non-aromatic carbon-carbon double bonds may be present. Thus, "C_2-C_6 alkenyl" means an alkenyl radical having from 2 to 6 carbon atoms. Alkenyl groups include ethenyl, propenyl, butenyl, 2-methylbutenyl and cyclohexenyl. The straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Thus, "C_2-C_6 alkynyl" means an alkynyl radical having from 2 to 6 carbon atoms. Alkynyl groups include ethynyl, propynyl, butynyl, 3-methylbutynyl and so on. The straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated.

In certain instances, substituents may be defined with a range of carbons that includes zero, such as (C_0-C_6)alkylene-aryl. If aryl is taken to be phenyl, this definition would include phenyl itself as well as -CH_2Ph, -CH_2CH_2Ph, $CH(CH_3)CH_2CH(CH_3)$Ph, and so on.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl and biphenyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring.

The term heteroaryl, as used herein, represents a stable monocyclic or bicyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrrazolyl, indolyl, benzotriazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinoline. As with the definition of heterocycle below, "heteroaryl" is also understood to include the N-oxide derivative of any nitrogen-containing heteroaryl. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively.

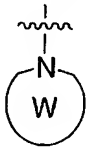
The term "heterocycle" or "heterocyclyl" as used herein is intended to mean a 5- to 10-membered aromatic or nonaromatic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of O, N and S, and includes bicyclic groups. "Heterocyclyl" therefore includes the above mentioned heteroaryls, as well as dihydro and tetrathydro analogs thereof. Further examples of "heterocyclyl" include, but are not limited to the following: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyridin-2-onyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl,

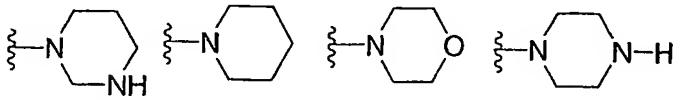
dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof. Attachment of a heterocyclyl substituent can occur via a carbon atom or via a heteroatom.

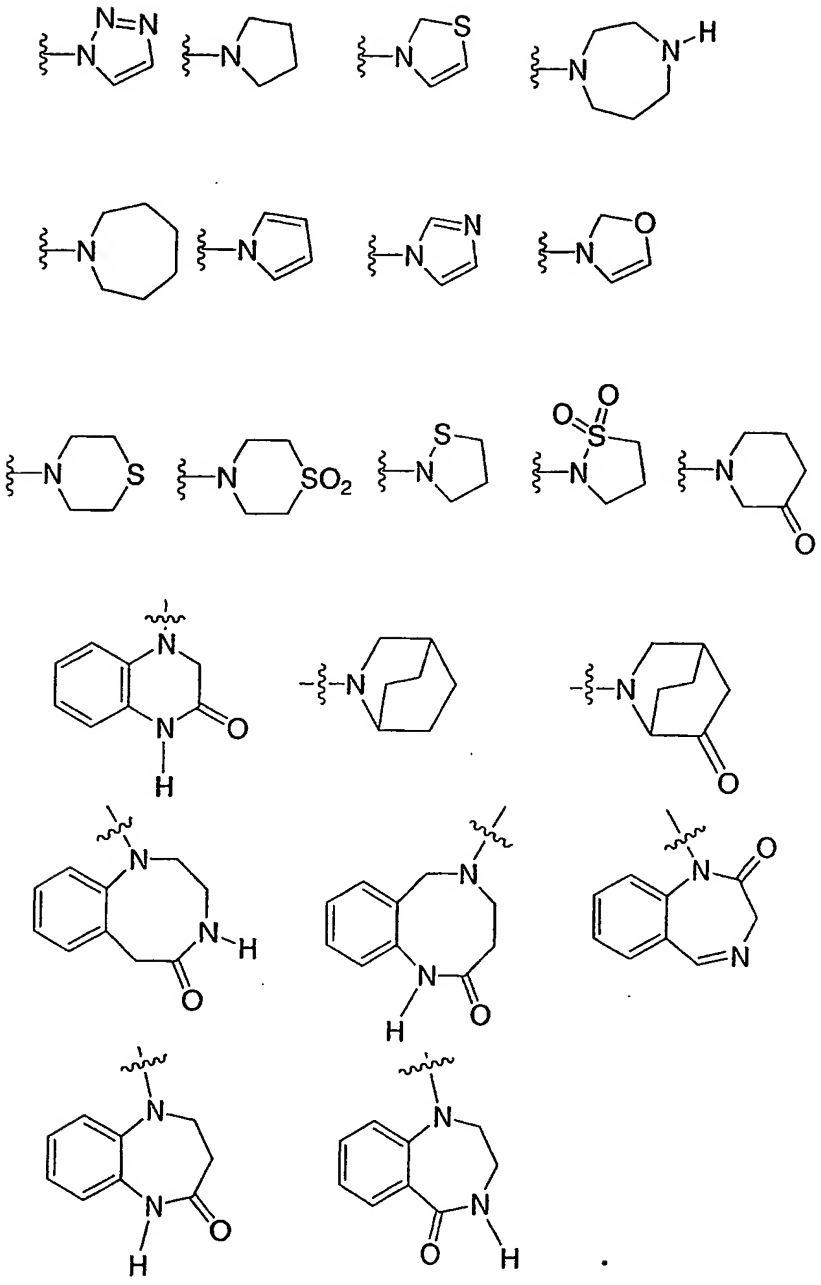
Preferably, heterocycle is selected from 2-azepinone, benzimidazolyl, 2-diazapinone, imidazolyl, 2-imidazolidinone, indolyl, isoquinolinyl, morpholinyl, piperidyl, piperazinyl, pyridyl, pyrrolidinyl, 2-piperidinone, 2-pyrimidinone, 2-pyrollidinone, quinolinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, and thienyl.

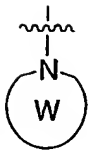
As appreciated by those of skill in the art, "halo" or "halogen" as used herein is intended to include chloro, fluoro, bromo and iodo.

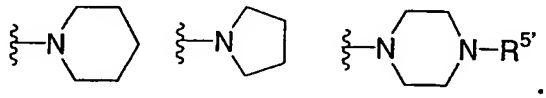
The alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl substituents may be unsubstituted or unsubstituted, unless specifically defined otherwise. For example, a (C_1-C_6)alkyl may be substituted with one, two or three substituents selected from OH, oxo, halogen, alkoxy, dialkylamino, or heterocyclyl, such as morpholinyl, piperidinyl, and so on. In this case, if one substituent is oxo and the other is OH, the following are included in the definition: -C=O)$CH_2CH(OH)CH_3$, -(C=O)OH, -$CH_2(OH)CH_2CH(O)$, and so on.

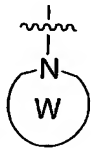
Examples of the group  include, but are not limited, to the following, keeping in mind that the heterocycle W is optionally substituted with one, two or three substituents chosen from R^5:

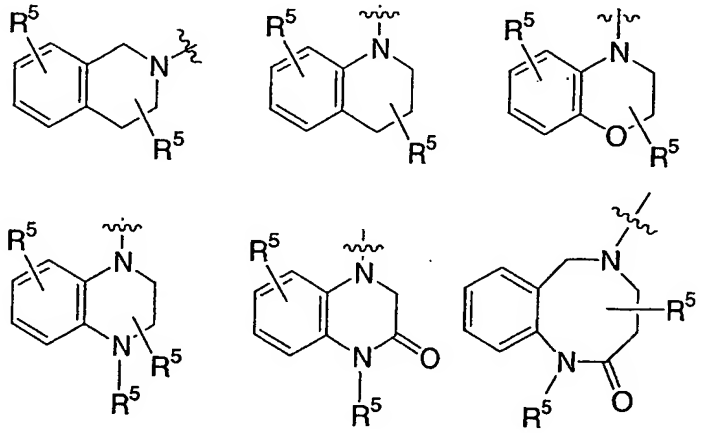




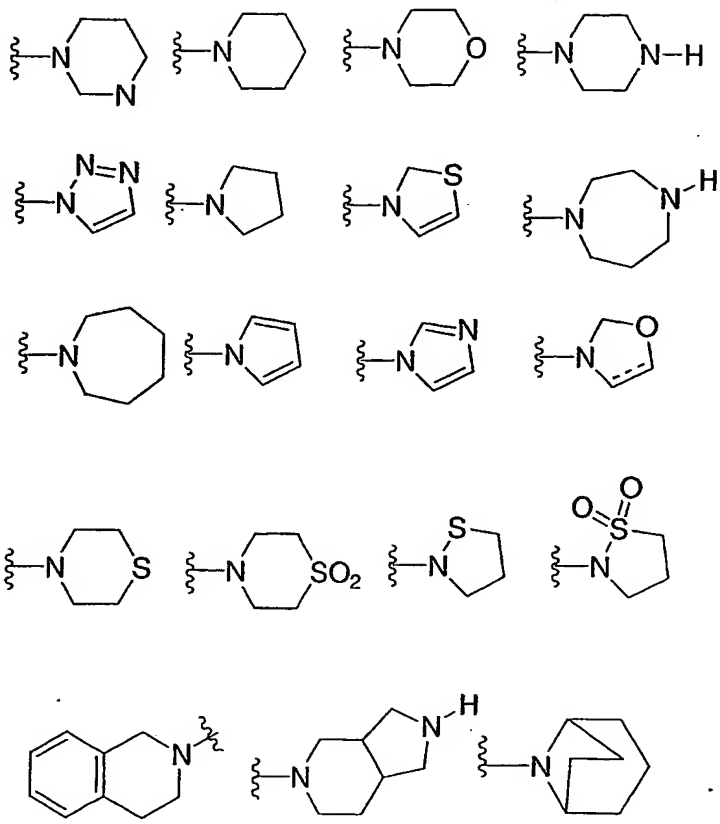
In a preferred embodiment, the group  is selected from the following, keeping in mind that the heterocycle W is optionally substituted with one, two or three substituents chosen from R^5:



In another preferred embodiment, the group  is selected from the following, keeping in mind that the heterocycle W is optionally substituted with one, two or three substituents chosen from R^5:



In certain instances, R^7 and R^8 are defined such that they can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said heterocycle optionally substituted with one or more substituents selected from R^{6a}. Examples of the heterocycles that can thus be formed include, but are not limited to the following, keeping in mind that the heterocycle is optionally substituted with one or more (and preferably one, two or three) substituents chosen from R^6:



Preferably R^1 is selected from: H, $(C_1\text{-}C_6)$alkyl, aryl and aryl $(C_1\text{-}C_6)$ alkyl. More preferably, R^1 is benzyl, optionally substituted with one to three substituents selected from R^5.

Preferably R^2 is selected from: $(C_1\text{-}C_6)$alkyl, aryl and aryl$(C_1\text{-}C_6)$ alkyl. More preferably, R^2 is $C_2\text{-}C_6$-alkyl.

Also prefered is the definition of R^3 as H.

Preferably R^5 is defined as halo, $C_1\text{-}C_6$ alkyl, $OC_1\text{-}C_6$ alkylene NR^7R^8, $(C{=}O)_aC_0\text{-}C_6$ alkylene-Q, (wherein Q is H, OH, CO_2H, or $OC_1\text{-}C_6$ alkyl), SO_2NH_2, $C_1\text{-}C_6$ alkyleneNR^{7}R^8 or $OC_0\text{-}C_6$ alkylene-heterocyclyl, optionally substituted with one to three substituents selected from R^6, $C_0\text{-}C_6$ alkyleneNR^{7}R^8, $(C{=}O)NR^7R^8$, or $OC_1\text{-}C_3$ alkylene-$(C{=}O)NR^7R^8$. Most preferably R^5 is halo, $C_1\text{-}C_6$ alkyl or $C_1\text{-}C_3$ alkyleneNR^{7}R^8.

Included in the instant invention is the free form of compounds of Formula I, as well as the pharmaceutically acceptable salts and stereoisomers thereof. Some of the specific compounds exemplified herein are the protonated salts of amine compounds. The term "free form" refers to the amine compounds in non-salt form. The encompassed pharmaceutically acceptable salts not only include the salts exemplified for the specific compounds described herein, but also all the typical pharmaceutically acceptable salts of the free form of compounds of Formula I. The free form of the specific salt compounds described may be isolated using techniques known in the art. For example, the free form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free forms may differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise pharmaceutically equivalent to their respective free forms for purposes of the invention.

The pharmaceutically acceptable salts of the instant compounds can be synthesized from the compounds of this invention which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the appropriate inorganic or organic base.

Thus, pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed by reacting a basic instant compound with an inorganic or organic acid. For example, conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like, as well as salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

When the compound of the present invention is acidic, suitable "pharmaceutically acceptable salts" refers to salts prepared form pharmaceutically

acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine caffeine, choline, N,N^1-dibenzylethylenediamine, diethylamin, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine tripropylamine, tromethamine and the like.

The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg *et al.*, "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977:66:1-19.

It will also be noted that the compounds of the present invention are potentially internal salts or zwitterions, since under physiological conditions a deprotonated acidic moiety in the compound, such as a carboxyl group, may be anionic, and this electronic charge might then be balanced off internally against the cationic charge of a protonated or alkylated basic moiety, such as a quaternary nitrogen atom.

The compounds of this invention may be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature or exemplified in the experimental procedures. For example, as described in Ager et al., J. of Med. Chem., 20:379-386 (1977), hereby incorporated by reference, quinazolinones can be obtained by acid-catalyzed condensation of N-acylanthranilic acids with aromatic primary amines. Other processes for preparing quinazolinones are described in U.S. Patent applications 5,783,577, 5,922,866 and 5,187,167, all of which are incorporated by reference. The illustrative schemes below, therefore, are not limited by the compounds listed or by any particular substituents employed for illustrative purposes. Substituent numbering as shown in the schemes does not necessarily correlate to that used in the claims and often, for clarity, a single substituent is shown attached to the

compound where multiple substituents are allowed under the definitions of Formula I hereinabove.

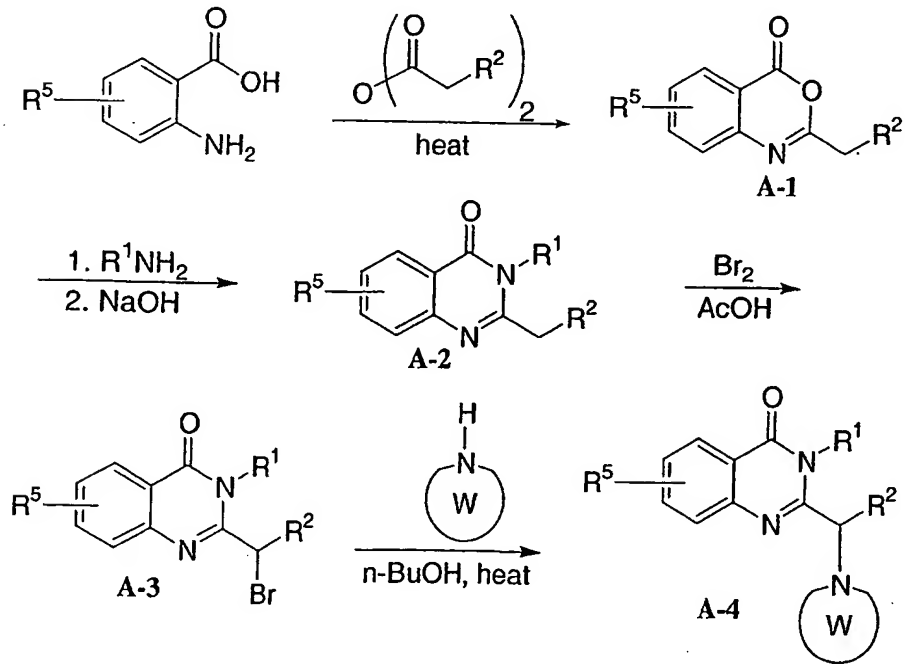
SCHEMES

As shown in Scheme A, the 2-bromomethylquinazolinone reagent **A-3** can be synthesized starting with a suitably substituted anthranilic acid. A variety of suitably substituted cyclic amines can then be used to displace the bromide, providing the instant compound A-4.

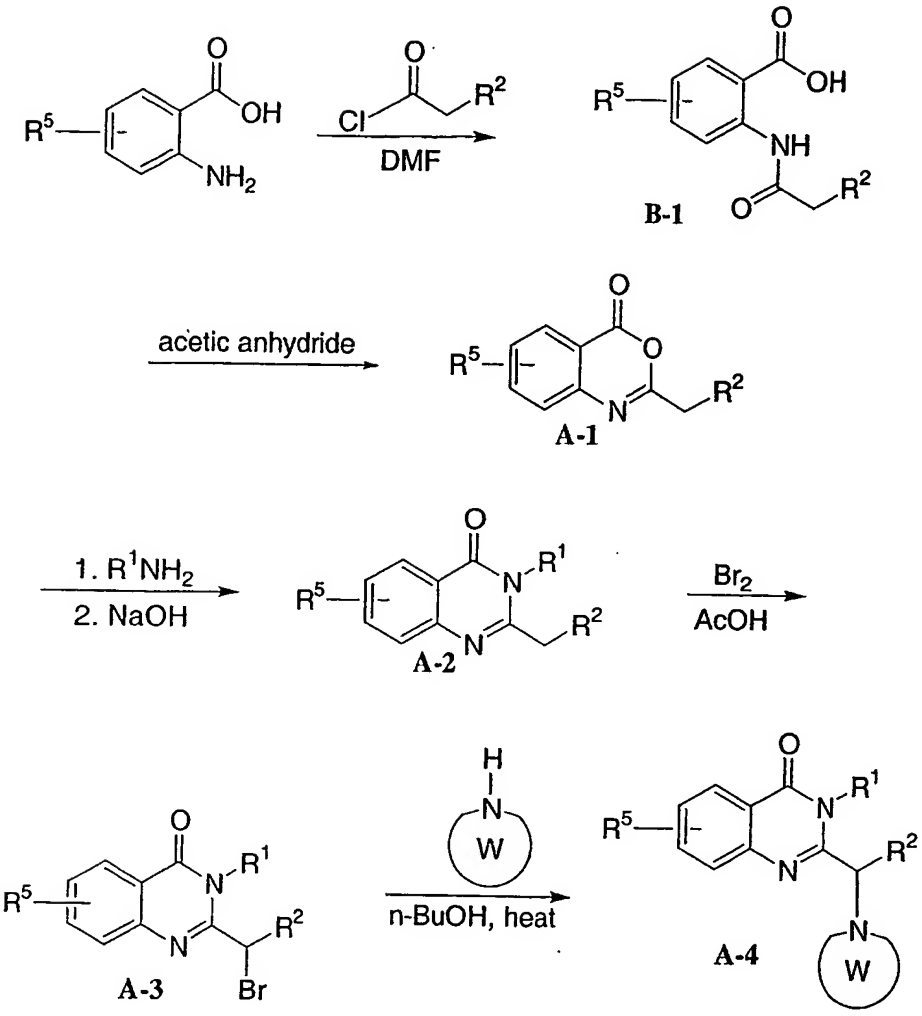
Scheme B illustrates an alternative two step synthetic route for the preparation of the 4H-3,1-benzoxazin-4-one intermediate A-1.

Scheme C illustrates incorporation of the preferred substituents R^1 = benzyl and R^2 = alkyl.

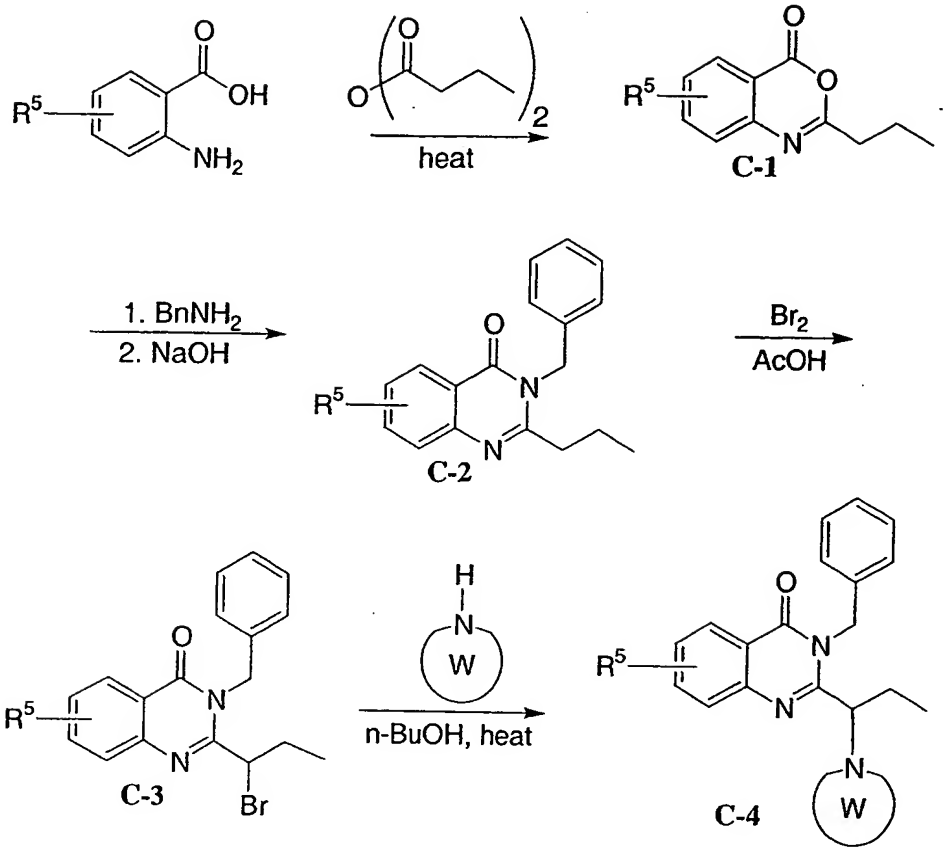
SCHEME A



SCHEME B


R5
OH
NH2
Cl
R2
DMF
NH
B-1
acetic anhydride
A-1
1. R1NH2
2. NaOH
A-2
Br2
AcOH
A-3
Br
H
N
W
n-BuOH, heat
A-4

SCHEME C



Utilities

The compounds of the invention find use in a variety of applications. As will be appreciated by those in the art, mitosis may be altered in a variety of ways; that is, one can affect mitosis either by increasing or decreasing the activity of a component in the mitotic pathway. Stated differently, mitosis may be affected (e.g., disrupted) by disturbing equilibrium, either by inhibiting or activating certain components. Similar approaches may be used to alter meiosis.

In a preferred embodiment, the compounds of the invention are usedto modulate mitotic spindle formation, thus causing prolonged cell cycle arrest in

mitosis. By " modulate" herein is meant altering mitotic spindle formation, including increasing and decreasing spindle formation. By "mitotic spindle formation" herein is meant organization of microtubules into bipolar structures by mitotic kinesins. By "mitotic spindle dysfunction" herein is meant mitotic arrest and monopolar spindle formation.

The compounds of the invention are useful to bind to and/or modulate the activity of a mitotic kinesin. In a preferred embodiment, the mitotic kinesin is a member of the bimC subfamily of mitotic kinesins (as described in U.S. Patent No. 6,284,480, column 5). In a further preferred embodiment, the mitotic is human KSP, although the activity of mitotic kinesins from other organisms may also be modulated by the compounds of the present invention. In this context, modulate means either increasing or decreasing spindle pole separation, causing malformation, i.e., splaying, of mitotic spindle poles, or otherwise causing morphological perturbation of the mitotic spindle. Also included within the definition of KSP for these purposes are variants and/or fragments of KSP. See PCT Publ. WO 01/31335: "Methods of Screening for Modulators of Cell Proliferation and Methods of Diagnosing Cell Proliferation States", filed Oct. 27, 1999, hereby incorporated by reference in its entirety. In addition, other mitotic kinesins may be inhibited by the compounds of the present invention.

The compounds of the invention are used to treat cellular proliferation diseases. Disease states which can be treated by the methods and compositions provided herein include, but are not limited to, cancer (further discussed below), autoimmune disease, arthritis, graft rejection, inflammatory bowel disease, proliferation induced after medical procedures, including, but not limited to, surgery, angioplasty, and the like. It is appreciated that in some cases the cells may not be in a hyper or hypo, proliferation state (abnormal state) and still require treatment. For example, during wound healing, the cells may be proliferating "normally", but proliferation enhancement may be desired. Similarly, as discussed above, in the agriculture arena, cells may be in a "normal" state, but proliferation modulation may be desired to enhance a crop by directly enhancing growth of a crop, or by inhibiting the growth of a plant or organism which adversely affects the crop. Thus, in one embodiment, the invention herein includes application to cells or individuals afflicted or impending affliction with any one of these disorders or states.

The compounds, compositions and methods provided herein are particularly deemed useful for the treatment of cancer including solid tumors such as skin, breast, brain, cervical carcinomas, testicular carcinomas, etc. More particularly, cancers that may be treated by the compounds, compositions and methods of the invention include, but are not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple mycloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous

cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above identified conditions.

The compounds of the instant invention may also be useful as antifungal agents, by modulating the activity of the fungal members of the bimC kinesin subgroup, as is described in in U.S. Patent No. 6,284,480.

The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

Additionally, the compounds of the instant invention may be administered to a mammal in need thereof using a gel extrusion mechanism (GEM) device, such as that described in USSN 60/144,643, filed on July 20, 1999, which is hereby incorporated by reference.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specific amounts, as well as any product which results, directly or indirectly, from combination of the specific ingredients in the specified amounts.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and

such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropyl-methylcellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, cellulose acetate buryrate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous

suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For

example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulation.

The injectable solutions or microemulsions may be introduced into a patient's blood-stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of Formula I may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal

delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, sex and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

The instant compounds may also be co-administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated.

For example, instant compounds are useful in combination with known anti-cancer agents. Combinations of the presently disclosed compounds with other anti-cancer or chemotherapeutic agents are within the scope of the invention. Examples of such agents can be found in *Cancer Principles and Practice of Oncology* by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Such anti-cancer agents include the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors and other angiogenesis inhibitors and agents that interfere with cell cycle checkpoints. The instant compounds are particularly useful when co-administered with radiation therapy.

"Estrogen receptor modulators" refers to compounds that interfere with or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-

dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

"Androgen receptor modulators" refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5α-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

"Retinoid receptor modulators" refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α-difluoromethylornithine, ILX23-7553, trans-N-(4'-hydroxyphenyl) retinamide, and N-4-carboxyphenyl retinamide.

"Cytotoxic/cytostatic agents" refer to compounds which cause cell death or inhibit cell proliferation primarily by interfering directly with the cell's functioning or inhibit or interfere with cell myosis, including alkylating agents, tumor necrosis factors, intercalators, hypoxia activatable compounds, microtubule inhibitors/microtubule-stabilising agents, inhibitors of mitotic kinesins, anti-metabolites; biological response modifiers; hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, monoclonal antibody targeted therapeutic agents and topoisomerase inhibitors.

Examples of cytotoxic agents include, but are not limited to, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro)platinum (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, and 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin (see WO 00/50032).

An example of a hypoxia activatable compound is tirapazamine.

Examples of microtubule inhibitors/microtubule-stabilising agents include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincaleukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, the epothilones (see for example U.S. Pat. Nos. 6,284,781 and 6,288,237) and BMS188797.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H) propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':b,7]-indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a, 5aB, 8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydro0xy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexohydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, N-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c] quinolin-7-one, and dimesna.

Examples of inhibitors of mitotic kinesins are described in PCT Publications WO 01/30768 and WO 01/98278.

"Antiproliferative agents" includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed,

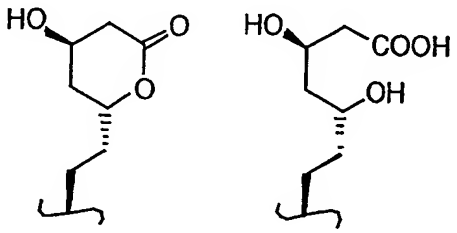
pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin; 5-flurouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine, 3-aminopyridine-2-carboxaldehyde thiosemicarbazone and trastuzumab.

Examples of monoclonal antibody targeted therapeutic agents include those therapeutic agents which have cytotoxic agents or radioisotopes attached to a cancer cell specific or target cell specific monoclonal antibody. Examples include Bexxar.

"HMG-CoA reductase inhibitors" refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Patent 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33. The terms "HMG-CoA reductase inhibitor" and "inhibitor of HMG-CoA reductase" have the same meaning when used herein.

Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see U.S. Patent Nos. 4,231,938, 4,294,926 and 4,319,039), simvastatin (ZOCOR®; see U.S. Patent Nos. 4,444,784, 4,820,850 and 4,916,239), pravastatin (PRAVACHOL®; see U.S. Patent Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589), fluvastatin (LESCOL®; see U.S. Patent Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and 5,356,896), atorvastatin (LIPITOR®; see U.S. Patent Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952) and cerivastatin (also known as rivastatin and BAYCHOL®; see US Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form

the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention. An illustration of the lactone portion and its corresponding open-acid form is shown below as structures I and II.



Lactone
I

Open-Acid
II

In HMG-CoA reductase inhibitors where an open-acid form can exist, salt and ester forms may preferably be formed from the open-acid, and all such forms are included within the meaning of the term "HMG-CoA reductase inhibitor" as used herein. Preferably, the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin, and most preferably simvastatin. Herein, the term "pharmaceutically acceptable salts" with respect to the HMG-CoA reductase inhibitor shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium, as well as those salts formed from amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenz-imidazole, diethylamine, piperazine, and tris(hydroxymethyl) aminomethane. Further examples of salt forms of HMG-CoA reductase inhibitors may include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate,

napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate.

Ester derivatives of the described HMG-CoA reductase inhibitor compounds may act as prodrugs which, when absorbed into the bloodstream of a warm-blooded animal, may cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

"Prenyl-protein transferase inhibitor" refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase). Examples of prenyl-protein transferase inhibiting compounds include (±)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone, (-)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone, (+)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl) methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone, 5(S)-n-butyl-1-(2,3-dimethylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone, (S)-1-(3-chlorophenyl) -4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl) methyl)-2-piperazinone, 5(S)-n-Butyl-1-(2-methylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone, 1-(3-chlorophenyl) -4-[1-(4-cyanobenzyl)-2-methyl-5-imidazolylmethyl]-2-piperazinone, 1-(2,2-diphenylethyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl]piperidine, 4-{5-[4-hydroxymethyl-4-(4-chloropyridin-2-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl} benzonitrile, 4-{5-[4-hydroxymethyl-4-(3-chlorobenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile, 4-{3-[4-(2-oxo-2H-pyridin-1-yl)benzyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-{3-[4-(5-chloro-2-oxo-2H-[1,2']bipyridin-5'-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-{3-[4-(2-oxo-2H-[1,2'] bipyridin-5'-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl}benzonitrile, 18,19-dihydro-19-oxo-5*H*,17*H*-6,10:12,16-dimetheno-1H-imidazo[4,3-*c*][1,11,4]dioxaazacyclo-nonadecine-9-carbonitrile, (±)-19,20-dihydro-19-oxo-5*H*-18,21-ethano-12,14-etheno-6,10-metheno-22*H*-benzo[*d*]imidazo[4,3-*k*][1,6,9,12]oxatriaza-cyclooctadecine-9-carbonitrile, 19,20-dihydro-19-oxo-5*H*,17*H*-

18,21-ethano-6,10:12,16-dimetheno-22*H*-imidazo[3,4-*h*][1,8,11,14]oxatriazacycloeicosine-9-carbonitrile, and (±)-19,20-dihydro-3-methyl-19-oxo-5*H*-18,21-ethano-12,14-etheno-6,10-metheno-22*H*-benzo [*d*]imidazo[4,3-*k*][1,6,9,12]oxa-triazacyclooctadecine-9-carbonitrile.

Other examples of prenyl-protein transferase inhibitors can be found in the following publications and patents: WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/29119, WO 95/32987, U.S. Patent No. 5,420,245, U.S. Patent No. 5,523,430, U.S. Patent No. 5,532,359, U.S. Patent No. 5,510,510, U.S. Patent No. 5,589,485, U.S. Patent No. 5,602,098, European Patent Publ. 0 618 221, European Patent Publ. 0 675 112, European Patent Publ. 0 604 181, European Patent Publ. 0 696 593, WO 94/19357, WO 95/08542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, U.S. Patent No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, U.S. Patent No. 5,571,792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO 96/31111, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, and U.S. Patent No. 5,532,359. For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see European J. of Cancer, Vol. 35, No. 9, pp.1394-1401 (1999).

"Angiogenesis inhibitors" refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR2), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon-α, interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxygenase-2 inhibitors like celecoxib and rofecoxib (PNAS, Vol. 89, p. 7384 (1992); JNCI, Vol. 69, p. 475 (1982); Arch. Opthalmol., Vol. 108, p.573 (1990); Anat. Rec., Vol. 238, p. 68 (1994); FEBS Letters, Vol. 372, p. 83 (1995); Clin, Orthop. Vol. 313,

p. 76 (1995); J. Mol. Endocrinol., Vol. 16, p.107 (1996); Jpn. J. Pharmacol., Vol. 75, p. 105 (1997); Cancer Res., Vol. 57, p. 1625 (1997); Cell, Vol. 93, p. 705 (1998); Intl. J. Mol. Med., Vol. 2, p. 715 (1998); J. Biol. Chem., Vol. 274, p. 9116 (1999)), steroidal anti-inflammatories (such as corticosteroids, mineralocorticoids, dexamethasone, prednisone, prednisolone, methylpred, betamethasone), carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see Fernandez et al., J. Lab. Clin. Med. 105:141-145 (1985)), and antibodies to VEGF (see, Nature Biotechnology, Vol. 17, pp.963-968 (October 1999); Kim et al., Nature, *362*, 841-844 (1993); WO 00/44777; and WO 00/61186).

Other therapeutic agents that modulate or inhibit angiogenesis and may also be used in combination with the compounds of the instant invention include agents that modulate or inhibit the coagulation and fibrinolysis systems (see review in *Clin. Chem. La. Med.* 38:679-692 (2000)). Examples of such agents that modulate or inhibit the coagulation and fibrinolysis pathways include, but are not limited to, heparin (see *Thromb. Haemost.* 80:10-23 (1998)), low molecular weight heparins and carboxypeptidase U inhibitors (also known as inhibitors of active thrombin activatable fibrinolysis inhibitor [TAFIa]) (see *Thrombosis Res.* 101:329-354 (2001)). TAFIa inhibitors have been described in U.S. Ser. Nos. 60/310,927 (filed August 8, 2001) and 60/349,925 (filed January 18, 2002).

"Agents that interfere with cell cycle checkpoints" refer to compounds that inhibit protein kinases, that transduce the cell cycle checkpoint signals, and prevent cell cycle arrest and DNA repair, thereby sensitizing the cancer cell to DNA damaging agents. Such agents include inhibitors of ATR, ATM, the Chk1 and Chk2 kinases and cdk and cdc kinase inhibitors and are specifically exemplified by 7-hydroxystaurosporin, flavopiridol, CYC202 (Cyclacel) and BMS-387032.

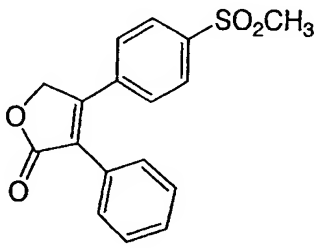
As described above, the combinations with NSAID's are directed to the use of NSAID's which are potent COX-2 inhibiting agents. For purposes of this specification an NSAID is potent if it possess an IC_{50} for the inhibition of COX-2 of 1μM or less as measured by cell or microsomal assays.

The invention also encompasses combinations with NSAID's which are selective COX-2 inhibitors. For purposes of this specification NSAID's which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least 100 fold as measured by the ratio of IC_{50}

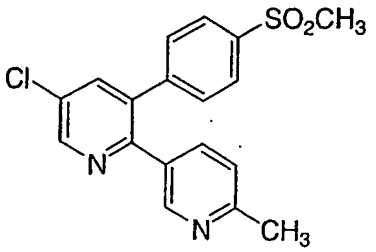
for COX-2 over IC_{50} for COX-1 evaluated by cell or microsomal assays. Such compounds include, but are not limited to those disclosed in U.S. Patent 5,474,995, issued December 12, 1995, U.S. Patent 5,861,419, issued January 19, 1999, U.S. Patent 6,001,843, issued December 14, 1999, U.S. Patent 6,020,343, issued February 1, 2000, U.S. Patent 5,409,944, issued April 25, 1995, U.S. Patent 5,436,265, issued July 25, 1995, U.S. Patent 5,536,752, issued July 16, 1996, U.S. Patent 5,550,142, issued August 27, 1996, U.S. Patent 5,604,260, issued February 18, 1997, U.S. 5,698,584, issued December 16, 1997, U.S. Patent 5,710,140, issued January 20,1998, WO 94/15932, published July 21, 1994, U.S. Patent 5,344,991, issued June 6, 1994, U.S. Patent 5,134,142, issued July 28, 1992, U.S. Patent 5,380,738, issued January 10, 1995, U.S. Patent 5,393,790, issued February 20, 1995, U.S. Patent 5,466,823, issued November 14, 1995, U.S. Patent 5,633,272, issued May 27, 1997, and U.S. Patent 5,932,598, issued August 3, 1999, all of which are hereby incorporated by reference.

Inhibitors of COX-2 that are particularly useful in the instant method of treatment are:

3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone; and



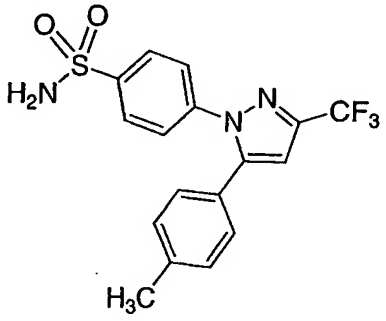
5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine;

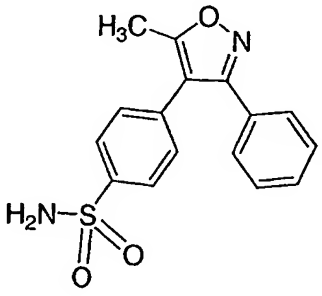


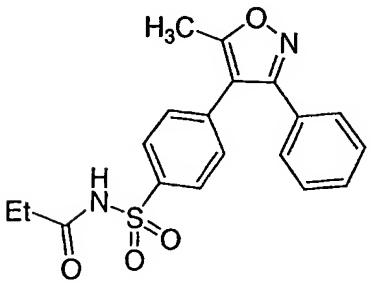
or a pharmaceutically acceptable salt thereof.

General and specific synthetic procedures for the preparation of the COX-2 inhibitor compounds described above are found in U.S. Patent No. 5,474,995, issued December 12, 1995, U.S. Patent No. 5,861,419, issued January 19, 1999, and U.S. Patent No. 6,001,843, issued December 14, 1999, all of which are herein incorporated by reference.

Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to, the following:







or a pharmaceutically acceptable salt thereof.

Compounds which are described as specific inhibitors of COX-2 and are therefore useful in the present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications, which are herein incorporated by reference: WO 94/15932, published July 21, 1994, U.S. Patent No. 5,344,991, issued June 6, 1994, U.S. Patent No. 5,134,142, issued July 28, 1992, U.S. Patent No. 5,380,738, issued January 10, 1995, U.S. Patent No. 5,393,790, issued February 20, 1995, U.S. Patent No. 5,466,823, issued November 14, 1995, U.S. Patent No. 5,633,272, issued May 27, 1997, and U.S. Patent No. 5,932,598, issued August 3, 1999.

Compounds which are specific inhibitors of COX-2 and are therefore useful in the present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications, which are herein incorporated by reference: U.S. Patent No. 5,474,995, issued December 12, 1995, U.S. Patent No. 5,861,419, issued January 19, 1999, U.S. Patent No. 6,001,843, issued December 14, 1999, U.S. Patent No. 6,020,343, issued February 1, 2000, U.S. Patent No. 5,409,944, issued April 25, 1995, U.S. Patent No. 5,436,265, issued July 25, 1995, U.S. Patent No. 5,536,752, issued July 16, 1996, U.S. Patent No. 5,550,142, issued August 27, 1996, U.S. Patent No. 5,604,260, issued February 18, 1997, U.S. Patent No. 5,698,584, issued December 16, 1997, and U.S. Patent No. 5,710,140, issued January 20,1998.

Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1H-1,2,3-triazole-4-carboxamide,CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[imino-N-methyl-4,2-pyrrolocarbonylimino[N-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

As used above, "integrin blockers" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha v\beta 5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or

counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins.

Some specific examples of tyrosine kinase inhibitors include N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl)indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxyl]quinazoline, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH268, genistein, STI571, CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, STI571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamine, and EMD121974.

Combinations with compounds other than anti-cancer compounds are also encompassed in the instant methods. For example, combinations of the instantly claimed compounds with PPAR-γ (i.e., PPAR-gamma) agonists and PPAR-δ (i.e., PPAR-delta) agonists are useful in the treatment of certain malingnancies. PPAR-γ and PPAR-δ are the nuclear peroxisome proliferator-activated receptors γ and δ. The expression of PPAR-γ on endothelial cells and its involvement in angiogenesis has been reported in the literature (see *J. Cardiovasc. Pharmacol.* 1998; 31:909-913; *J. Biol. Chem.* 1999;274:9116-9121; *Invest. Ophthalmol Vis. Sci.* 2000; 41:2309-2317). More recently, PPAR-γ agonists have been shown to inhibit the angiogenic response to VEGF in vitro; both troglitazone and rosiglitazone maleate inhibit the development of retinal neovascularization in mice. (*Arch. Ophthamol.* 2001; 119:709-717). Examples of PPAR-γ agonists and PPAR-γ/α agonists include, but are not limited to, thiazolidinediones (such as DRF2725, CS-011, troglitazone, rosiglitazone, and pioglitazone), fenofibrate, gemfibrozil, clofibrate, GW2570, SB219994, AR-H039242, JTT-501, MCC-555, GW2331, GW409544, NN2344, KRP297, NP0110, DRF4158, NN622, GI262570, PNU182716, DRF552926, 2-[(5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl)oxy]-2-methylpropionic acid (disclosed in

USSN 09/782,856), and 2(R)-7-(3-(2-chloro-4-(4-fluorophenoxy) phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid (disclosed in USSN 60/235,708 and 60/244,697).

Another embodiment of the instant invention is the use of the presently disclosed compounds in combination with gene therapy for the treatment of cancer. For an overview of genetic strategies to treating cancer see Hall et al (Am J Hum Genet 61:785-789, 1997) and Kufe et al (Cancer Medicine, 5th Ed, pp 876-889, BC Decker, Hamilton 2000). Gene therapy can be used to deliver any tumor suppressing gene. Examples of such genes include, but are not limited to, p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Patent No. 6,069,134, for example), a uPA/uPAR antagonist ("Adenovirus-Mediated Delivery of a uPA/uPAR Antagonist Suppresses Angiogenesis-Dependent Tumor Growth and Dissemination in Mice," Gene Therapy, August 1998;5(8):1105-13), and interferon gamma (J Immunol 2000;164:217-222).

The compounds of the instant invention may also be administered in combination with an inhibitor of inherent multidrug resistance (MDR), in particular MDR associated with high levels of expression of transporter proteins. Such MDR inhibitors include inhibitors of p-glycoprotein (P-gp), such as LY335979, XR9576, OC144-093, R101922, VX853 and PSC833 (valspodar).

A compound of the present invention may be employed in conjunction with anti-emetic agents to treat nausea or emesis, including acute, delayed, late-phase, and anticipatory emesis, which may result from the use of a compound of the present invention, alone or with radiation therapy. For the prevention or treatment of emesis, a compound of the present invention may be used in conjunction with other anti-emetic agents, especially neurokinin-1 receptor antagonists, 5HT3 receptor antagonists, such as ondansetron, granisetron, tropisetron, and zatisetron, GABAB receptor agonists, such as baclofen, a corticosteroid such as Decadron (dexamethasone), Kenalog, Aristocort, Nasalide, Preferid, Benecorten or others such as disclosed in U.S.Patent Nos. 2,789,118, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and 3,749,712, an antidopaminergic, such as the phenothiazines (for example prochlorperazine, fluphenazine, thioridazine and mesoridazine), metoclopramide or dronabinol. For the treatment or prevention of emesis that may result upon administration of the instant compounds, conjunctive therapy with an anti-emesis agent selected from a neurokinin-1 receptor antagonist, a 5HT3 receptor antagonist and a corticosteroid is preferred.

Neurokinin-1 receptor antagonists of use in conjunction with the compounds of the present invention are fully described, for example, in U.S. Patent Nos. 5,162,339, 5,232,929, 5,242,930, 5,373,003, 5,387,595, 5,459,270, 5,494,926, 5,496,833, 5,637,699, 5,719,147; European Patent Publication Nos. EP 0 360 390, 0 394 989, 0 428 434, 0 429 366, 0 430 771, 0 436 334, 0 443 132, 0 482 539, 0 498 069, 0 499 313, 0 512 901, 0 512 902, 0 514 273, 0 514 274, 0 514 275, 0 514 276, 0 515 681, 0 517 589, 0 520 555, 0 522 808, 0 528 495, 0 532 456, 0 533 280, 0 536 817, 0 545 478, 0 558 156, 0 577 394, 0 585 913,0 590 152, 0 599 538, 0 610 793, 0 634 402, 0 686 629, 0 693 489, 0 694 535, 0 699 655, 0 699 674, 0 707 006, 0 708 101, 0 709 375, 0 709 376, 0 714 891, 0 723 959, 0 733 632 and 0 776 893; PCT International Patent Publication Nos. WO 90/05525, 90/05729, 91/09844, 91/18899, 92/01688, 92/06079, 92/12151, 92/15585, 92/17449, 92/20661, 92/20676, 92/21677, 92/22569, 93/00330, 93/00331, 93/01159, 93/01165, 93/01169, 93/01170, 93/06099, 93/09116, 93/10073, 93/14084, 93/14113, 93/18023, 93/19064, 93/21155, 93/21181, 93/23380, 93/24465, 94/00440, 94/01402, 94/02461, 94/02595, 94/03429, 94/03445, 94/04494, 94/04496, 94/05625, 94/07843, 94/08997, 94/10165, 94/10167, 94/10168, 94/10170, 94/11368, 94/13639, 94/13663, 94/14767, 94/15903, 94/19320, 94/19323, 94/20500, 94/26735, 94/26740, 94/29309, 95/02595, 95/04040, 95/04042, 95/06645, 95/07886, 95/07908, 95/08549, 95/11880, 95/14017, 95/15311, 95/16679, 95/17382, 95/18124, 95/18129, 95/19344, 95/20575, 95/21819, 95/22525, 95/23798, 95/26338, 95/28418, 95/30674, 95/30687, 95/33744, 96/05181, 96/05193, 96/05203, 96/06094, 96/07649, 96/10562, 96/16939, 96/18643, 96/20197, 96/21661, 96/29304, 96/29317, 96/29326, 96/29328, 96/31214, 96/32385, 96/37489, 97/01553, 97/01554, 97/03066, 97/08144, 97/14671, 97/17362, 97/18206, 97/19084, 97/19942 and 97/21702; and in British Patent Publication Nos. 2 266 529, 2 268 931, 2 269 170, 2 269 590, 2 271 774, 2 292 144, 2 293 168, 2 293 169, and 2 302 689. The preparation of such compounds is fully described in the aforementioned patents and publications, which are incorporated herein by reference.

A particularly preferred neurokinin-1 receptor antagonist for use in conjunction with the compounds of the present invention is 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine, or a pharmaceutically acceptable salt thereof, which is described in U.S. Patent No. 5,719,147.

A compound of the instant invention may also be administered with an agent useful in the treatment of anemia. Such an anemia treatment agent is, for example, a continuous eythropoiesis receptor activator (such as epoetin alfa).

A compound of the instant invention may also be administered with an agent useful in the treatment of neutropenia. Such a neutropenia treatment agent is, for example, a hematopoietic growth factor which regulates the production and function of neutrophils such as a human granulocyte colony stimulating factor, (G-CSF). Examples of a G-CSF include filgrastim.

A compound of the instant invention may also be administered with an immunologic-enhancing drug, such as levamisole, isoprinosine and Zadaxin.

Thus, the scope of the instant invention encompasses the use of the instantly claimed compounds in combination with a second compound selected from:

1) an estrogen receptor modulator,
2) an androgen receptor modulator,
3) retinoid receptor modulator,
4) a cytotoxic agent,
5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,
8) an HIV protease inhibitor,
9) a reverse transcriptase inhibitor,
10) an angiogenesis inhibitor,
11) PPAR-γ agonists,
12) PPAR-δ agonists,
13) an inhibitor of inherent multidrug resistance,
14) an anti-emetic agent,
15) an agent useful in the treatment of anemia,
16) agent useful in the treatment of neutropenia, and
17) an immunologic-enhancing drug.

Preferred angiogenesis inhibitors to be used as the second compound are a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP (matrix metalloprotease) inhibitor, an integrin blocker, interferon-α, interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor,

carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, or an antibody to VEGF. Preferred estrogen receptor modulators are tamoxifen and raloxifene.

Also included in the scope of the claims is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of Formula I in combination with radiation therapy and/or in combination with a compound selected from:

1) an estrogen receptor modulator,
2) an androgen receptor modulator,
3) retinoid receptor modulator,
4) a cytotoxic agent,
5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,
8) an HIV protease inhibitor,
9) a reverse transcriptase inhibitor,
10) an angiogenesis inhibitor,
11) PPAR-γ agonists,
12) PPAR-δ agonists,
13) an inhibitor of inherent multidrug resistance,
14) an anti-emetic agent,
15) an agent useful in the treatment of anemia,
16) agent useful in the treatment of neutropenia, and
17) an immunologic-enhancing drug.

And yet another embodiment of the invention is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of Formula I in combination with paclitaxel or trastuzumab.

The invention further encompasses a method of treating or preventing cancer that comprises administering a therapeutically effective amount of a compound of Formula I in combination with a COX-2 inhibitor.

The instant invention also includes a pharmaceutical composition useful for treating or preventing cancer that comprises a therapeutically effective amount of a compound of Formula I and a compound selected from:

1) an estrogen receptor modulator,

2) an androgen receptor modulator,
3) retinoid receptor modulator,
4) a cytotoxic agent,
5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,
8) an HIV protease inhibitor,
9) a reverse transcriptase inhibitor,
10) an angiogenesis inhibitor, and
11) a PPAR-γ agonist, and
12) PPAR-δ agonists.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

The term "treating cancer" or "treatment of cancer" refers to administration to a mammal afflicted with a cancerous condition and refers to an

effect that alleviates the cancerous condition by killing the cancerous cells, but also to an effect that results in the inhibition of growth and/or metastasis of the cancer.

The invention further comprises the use of the instant compounds in a method to screen for other compounds that bind to KSP. To employ the compounds of the invention in a method of screening for compounds that bind to KSP kinesin, the KSP is bound to a support, and a compound of the invention (which is a mitotic agent) is added to the assay. Alternatively, the compound of the invention is bound to the support and KSP is added. Classes of compounds among which novel binding agents may be sought include specific antibodies, non-natural binding agents identified in screens of chemical libraries, peptide analogs, etc. Of particular interest are screening assays for candidate agents that have a low toxicity for human cells. A wide variety of assays may be used for this purpose, including labeled *in vitro* protein-protein binding assays, electrophoretic mobility shift assays, immunoassays for protein binding, functional assays (phosphorylation assays, etc.) and the like.

The determination of the binding of the mitotic agent to KSP may be done in a number of ways. In a preferred embodiment, the mitotic agent (the compound of the invention) is labeled, for example, with a fluorescent or radioactive moiety and binding determined directly. For example, this may be done by attaching all or a portion of KSP to a solid support, adding a labeled mitotic agent (for example a compound of the invention in which at least one atom has been replaced by a detectable isotope), washing off excess reagent, and determining whether the amount of the label is that present on the solid support. Various blocking and washing steps may be utilized as is known in the art.

By "labeled" herein is meant that the compound is either directly or indirectly labeled with a label which provides a detectable signal, e.g., radioisotope, fluorescent tag, enzyme, antibodies, particles such as magnetic particles, chemiluminescent tag, or specific binding molecules, etc. Specific binding molecules include pairs, such as biotin and streptavidin, digoxin and antidigoxin etc. For the specific binding members, the complementary member would normally be labeled with a molecule which provides for detection, in accordance with known procedures, as outlined above. The label can directly or indirectly provide a detectable signal.

In some embodiments, only one of the components is labeled. For example, the kinesin proteins may be labeled at tyrosine positions using ^{125}I, or with

fluorophores. Alternatively, more than one component may be labeled with different labels; using ^{125}I for the proteins, for example, and a fluorophor for the mitotic agents.

The compounds of the invention may also be used as competitors to screen for additional drug candidates. "Candidate bioactive agent" or "drug candidate" or grammatical equivalents as used herein describe any molecule, e.g., protein, oligopeptide, small organic molecule, polysaccharide, polynucleotide, etc., to be tested for bioactivity. They may be capable of directly or indirectly altering the cellular proliferation phenotype or the expression of a cellular proliferation sequence, including both nucleic acid sequences and protein sequences. In other cases, alteration of cellular proliferation protein binding and/or activity is screened. Screens of this sort may be performed either in the presence or absence of microtubules. In the case where protein binding or activity is screened, preferred embodiments exclude molecules already known to bind to that particular protein, for example, polymer structures such as microtubules, and energy sources such as ATP. Preferred embodiments of assays herein include candidate agents which do not bind the cellular proliferation protein in its endogenous native state termed herein as "exogenous" agents. In another preferred embodiment, exogenous agents further exclude antibodies to KSP.

Candidate agents can encompass numerous chemical classes, though typically they are organic molecules, preferably small organic compounds having a molecular weight of more than 100 and less than about 2,500 daltons. Candidate agents comprise functional groups necessary for structural interaction with proteins, particularly hydrogen bonding and lipophilic binding, and typically include at least an amine, carbonyl, hydroxyl, ether, or carboxyl group, preferably at least two of the functional chemical groups. The candidate agents often comprise cyclical carbon or heterocyclic structures and/or aromatic or polyaromatic structures substituted with one or more of the above functional groups. Candidate agents are also found among biomolecules including peptides, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogs or combinations thereof. Particularly preferred are peptides.

Candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides.

Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural or synthetically produced libraries and compounds are readily modified through conventional chemical, physical and biochemical means. Known pharmacological agents may be subjected to directed or random chemical modifications, such as acylation, alkylation, esterification, amidification to produce structural analogs.

Competitive screening assays may be done by combining KSP and a drug candidate in a first sample. A second sample comprises a mitotic agent, KSP and a drug candidate. This may be performed in either the presence or absence of microtubules, The binding of the drug candidate is determined for both samples, and a change, or difference in binding between the two samples indicates the presence of an agent capable of binding to KSP and potentially modulating its activity. That is, if the binding of the drug candidate is different in the second sample relative to the first sample, the drug candidate is capable of binding to KSP.

In a preferred embodiment, the binding of the candidate agent is determined through the use of competitive binding assays. In this embodiment, the competitor is a binding moiety known to bind to KSP, such as an antibody, peptide, binding partner, ligand, etc. Under certain circumstances, there may be competitive binding as between the candidate agent and the binding moiety, with the binding moiety displacing the candidate agent.

In one embodiment, the candidate agent is labeled. Either the candidate agent, or the competitor, or both, is added first to KSP for a time sufficient to allow binding, if present. Incubations may be performed at any temperature which facilitates optimal activity, typically between about 4 and about 40°C.

Incubation periods are selected for optimum activity, but may also be optimized to facilitate rapid high throughput screening. Typically between 0.1 and 1 hour will be sufficient. Excess reagent is generally removed or washed away. The second component is then added, and the presence or absence of the labeled component is followed, to indicate binding.

In a preferred embodiment, the competitor is added first, followed by the candidate agent. Displacement of the competitor is an indication the candidate agent is binding to KSP and thus is capable of binding to, and potentially modulating, the activity of KSP. In this embodiment, either component can be labeled. Thus, for example, if the competitor is labeled, the presence of label in the wash solution

indicates displacement by the agent. Alternatively, if the candidate agent is labeled, the presence of the label on the support indicates displacement.

In an alternative embodiment, the candidate agent is added first, with incubation and washing, followed by the competitor. The absence of binding by the competitor may indicate the candidate agent is bound to KSP with a higher affinity. Thus, if the candidate agent is labeled, the presence of the label on the support, coupled with a lack of competitor binding, may indicate the candidate agent is capable of binding to KSP.

It may be of value to identify the binding site of KSP. This can be done in a variety of ways. In one embodiment, once KSP has been identified as binding to the mitotic agent, KSP is fragmented or modified and the assays repeated to identify the necessary components for binding.

Modulation is tested by screening for candidate agents capable of modulating the activity of KSP comprising the steps of combining a candidate agent with KSP, as above, and determining an alteration in the biological activity of KSP. Thus, in this embodiment, the candidate agent should both bind to KSP (although this may not be necessary), and alter its biological or biochemical activity as defined herein. The methods include both in vitro screening methods and in vivo screening of cells for alterations in cell cycle distribution, cell viability, or for the presence, morpohology, activity, distribution, or amount of mitotic spindles, as are generally outlined above.

Alternatively, differential screening may be used to identify drug candidates that bind to the native KSP, but cannot bind to modified KSP.

Positive controls and negative controls may be used in the assays. Preferably all control and test samples are performed in at least triplicate to obtain statistically significant results. Incubation of all samples is for a time sufficient for the binding of the agent to the protein. Following incubation, all samples are washed free of non- specifically bound material and the amount of bound, generally labeled agent determined. For example, where a radiolabel is employed, the samples may be counted in a scintillation counter to determine the amount of bound compound.

A variety of other reagents may be included in the screening assays. These include reagents like salts, neutral proteins, e.g., albumin, detergents, etc which may be used to facilitate optimal protein-protein binding and/or reduce non-specific or background interactions. Also reagents that otherwise improve the efficiency of the

assay, such as protease inhibitors, nuclease inhibitors, anti-microbial agents, etc., may be used. The mixture of components may be added in any order that provides for the requisite binding.

These and other aspects of the invention will be apparent from the teachings contained herein.

ASSAYS

The compounds of the instant invention described in the Examples were tested by the assays described below and were found to have kinase inhibitory activity. Other assays are known in the literature and could be readily performed by those of skill in the art (see, for example, PCT Publication WO 01/30768, May 3, 2001, pages 18-22).

I. Kinesin ATPase *In Vitro* Assay

Cloning and expression of human poly-histidine tagged KSP motor domain (KSP(367H))

Plasmids for the expression of the human KSP motor domain construct were cloned by PCR using a pBluescript full length human KSP construct (Blangy et al., Cell, vol.83, pp1159-1169, 1995) as a template. The N-terminal primer 5'-GCAACGATTAATATGGCGTCGCAGCCAAATTCGTCTGCGAAG (SEQ.ID.NO.: 1) and the C-terminal primer 5'-GCAACGCTCGAGTCAGTGAT GATGGTGGTGATGCTGATTCACTTCAGGCTTATTCAATAT (SEQ.ID.NO.: 2) were used to amplify the motor domain and the neck linker region. The PCR products were digested with AseI and XhoI, ligated into the NdeI/XhoI digestion product of pRSETa (Invitrogen) and transformed into E. coli BL21 (DE3).

Cells were grown at 37°C to an OD_{600} of 0.5. After cooling the culture to room temperature expression of KSP was induced with 100μM IPTG and incubation was continued overnight. Cells were pelleted by centrifugation and washed once with ice-cold PBS. Pellets were flash-frozen and stored –80°C.

Protein Purification

Cell pellets were thawed on ice and resuspended in lysis buffer (50mM K-HEPES, pH 8.0, 250mM KCl, 0.1% Tween, 10mM imidazole, 0.5mM Mg-ATP,

1mM PMSF, 2mM benzimidine, 1x complete protease inhibitor cocktail (Roche)). Cell suspensions were incubated with 1mg/ml lysozyme and 5mM β-mercaptoethanol on ice for 10 minutes, followed by sonication (3x 30sec). All subsequent procedures were performed at 4°C. Lysates were centrifuged at 40,000x g for 40 minutes. Supernatants were diluted and loaded onto an SP Sepharose column (Pharmacia, 5ml cartridge) in buffer A (50mM K-HEPES, pH 6.8, 1mM $MgCl_2$, 1mM EGTA, 10μM Mg-ATP, 1mM DTT) and eluted with a 0 to 750mM KCl gradient in buffer A. Fractions containing KSP were pooled and incubated with Ni-NTA resin (Qiagen) for one hour. The resin was washed three times with buffer B (Lysis buffer minus PMSF and protease inhibitor cocktail), followed by three 15-minute incubations and washes with buffer B. Finally, the resin was incubated and washed for 15 minutes three times with buffer C (same as buffer B except for pH 6.0) and poured into a column. KSP was eluted with elution buffer (identical to buffer B except for 150mM KCl and 250mM imidazole). KSP-containing fractions were pooled, made 10% in sucrose, and stored at -80°C.

Microtubules are prepared from tubulin isolated from bovine brain. Purified tubulin (> 97% MAP-free) at 1 mg/ml is polymerized at 37°C in the presence of 10 μM paclitaxel, 1 mM DTT, 1 mM GTP in BRB80 buffer (80 mM K-PIPES, 1 mM EGTA, 1 mM $MgCl_2$ at pH 6.8). The resulting microtubules are separated from non-polymerized tubulin by ultracentrifugation and removal of the supernatant. The pellet, containing the microtubules, is gently resuspended in 10 μM paclitaxel, 1 mM DTT, 50 μg/ml ampicillin, and 5 μg/ml chloramphenicol in BRB80.

The kinesin motor domain is incubated with microtubules, 1 mM ATP (1:1 $MgCl_2$: Na-ATP), and compound at 23°C in buffer containing 80 mM K-HEPES (pH 7.0), 1 mM EGTA, 1 mM DTT, 1 mM $MgCl_2$, and 50 mM KCl. The reaction is terminated by a 2-10 fold dilution with a final buffer composition of 80 mM HEPES and 50 mM EDTA. Free phosphate from the ATP hydrolysis reaction is measured via a quinaldine red/ammonium molybdate assay by adding 150 μl of quench C buffer containing a 2:1 ratio of quench A:quench B. Quench A contains 0.1 mg/ml quinaldine red and 0.14% polyvinyl alcohol; quench B contains 12.3 mM ammonium molybdate tetrahydrate in 1.15 M sulfuric acid. The reaction is incubated for 10 minutes at 23°C, and the absorbance of the phospho-molybdate complex is measured at 540 nm.

The compounds 1-4 through 1-15 described in the Examples were tested in the above assay and found to have an $IC_{50} \leq 50\mu M$.

II. Cell Proliferation Assay

Cells are plated in 96-well tissue culture dishes at densities that allow for logarithmic growth over the course of 24, 48, and 72 hours and allowed to adhere overnight. The following day, compounds are added in a 10-point, one-half log titration to all plates. Each titration series is performed in triplicate, and a constant DMSO concentration of 0.1% is maintained throughout the assay. Controls of 0.1% DMSO alone are also included. Each compound dilution series is made in media without serum. The final concentration of serum in the assay is 5% in a 200 µL volume of media. Twenty microliters of Alamar blue staining reagent is added to each sample and control well on the titration plate at 24, 48, or 72 hours following the addition of drug and returned to incubation at 37°C. Alamar blue fluorescence is analyzed 6-12 hours later on a CytoFluor II plate reader using 530-560 nanometer wavelength excitation, 590 nanometer emission.

A cytotoxic EC_{50} is derived by plotting compound concentration on the x-axis and average percent inhibition of cell growth for each titration point on the y-axis. Growth of cells in control wells that have been treated with vehicle alone is defined as 100% growth for the assay, and the growth of cells treated with compounds is compared to this value. Proprietary in-house software is used calculate percent cytotoxicity values and inflection points using logistic 4-parameter curve fitting. Percent cytotoxicity is defined as:

$$\%\ \text{cytotoxicity}:(\text{Fluorescence}_{\text{control}}) - (\text{Flourescence}_{\text{sample}})\ x100x\ (\text{Fluorescence}_{\text{control}})^{-1}$$

The inflection point is reported as the cytotoxic EC_{50}.

III. Evaluation of mitotic arrest an

IV. d apoptosis by FACS

FACS analysis is used to evaluate the ability of a compound to arrest cells in mitosis and to induce apoptosis by measuring DNA content in a treated population of cells. Cells are seeded at a density of $1.4x10^6$ cells per $6cm^2$ tissue culture dish and allowed to adhere overnight. Cells are then treated with vehicle

(0.1% DMSO) or a titration series of compound for 8-16 hours. Following treatment, cells are harvested by trypsinization at the indicated times and pelleted by centrifugation. Cell pellets are rinsed in PBS and fixed in 70% ethanol and stored at 4°C overnight or longer.

For FACS analysis, at least 500,000 fixed cells are pelleted and the 70% ethanol is removed by aspiration. Cells are then incubated for 30 min at 4°C with RNase A (50 Kunitz units/ml) and propidium iodide (50 µg/ml), and analyzed using a Becton Dickinson FACSCaliber. Data (from 10,000 cells) is analyzed using the Modfit cell cycle analysis modeling software (Verity Inc.).

An EC_{50} for mitotic arrest is derived by plotting compound concentration on the x-axis and percentage of cells in the G2/M phase of the cell cycle for each titration point (as measured by propidium iodide fluorescence) on the y-axis. Data analysis is performed using the SigmaPlot program to calculate an inflection point using logistic 4-parameter curve fitting. The inflection point is reported as the EC_{50} for mitotic arrest. A similar method is used to determine the compound EC_{50}
for apoptosis. Here, the percentage of apoptotic cells at each titration point (as determined by propidium iodide fluorescence) is plotted on the y-axis, and a similar analysis is carried out as described above.

VI. Immunofluorescence Microscopy to Detect Monopolar Spindles

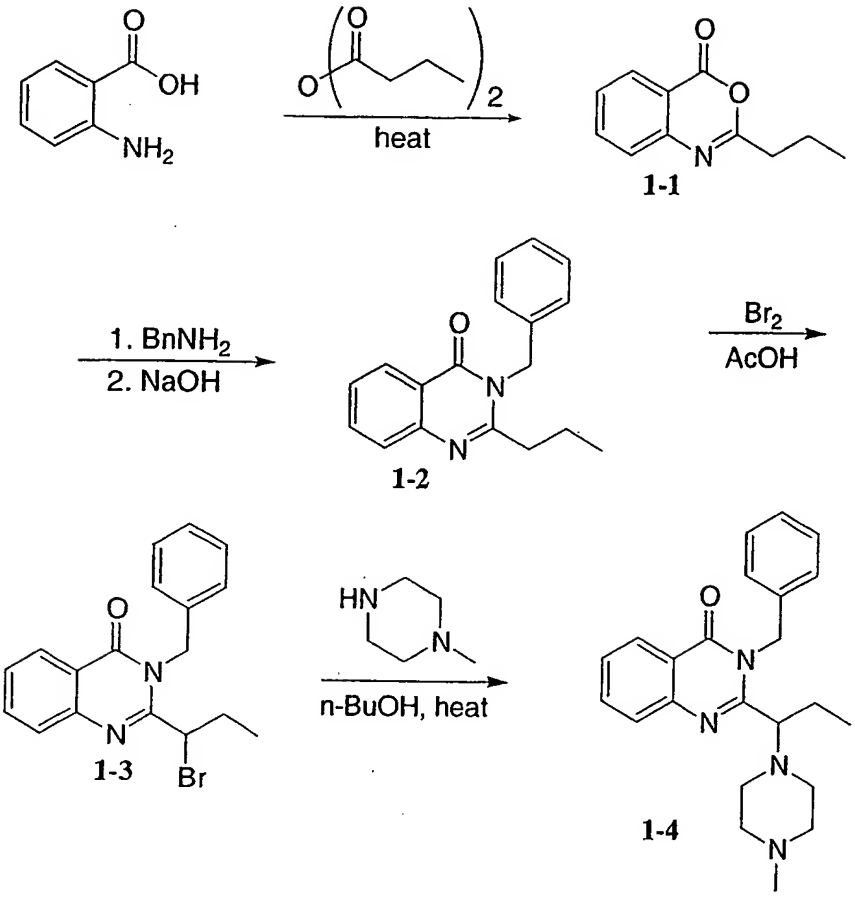
Methods for immunofluorescence staining of DNA, tubulin, and pericentrin are essentially as described in Kapoor *et al.* (2000) J. Cell Biol. **150**: 975-988. For cell culture studies, cells are plated on tissue-culture treated glass chamber slides and allowed to adhere overnight. Cells are then incubated with the compound of interest for 4 to 16 hours. After incubation is complete, media and drug are aspirated and the chamber and gasket are removed from the glass slide. Cells are then permeabilized, fixed, washed, and blocked for nonspecific antibody binding according to the referenced protocol. Paraffin-embedded tumor sections are deparaffinized with xylene and rehydrated through an ethanol series prior to blocking. Slides are incubated in primary antibodies (mouse monoclonal anti-α-tubulin antibody, clone DM1A from Sigma diluted 1:500; rabbit polyclonal anti-pericentrin antibody from Covance, diluted 1:2000) overnight at 4°C. After washing, slides are incubated with conjugated secondary antibodies (FITC-conjugated donkey anti-

mouse IgG for tubulin; Texas red-conjugated donkey anti-rabbit IgG for pericentrin) diluted to 15μg/ml for one hour at room temperature. Slides are then washed and counterstained with Hoechst 33342 to visualize DNA. Immunostained samples are imaged with a 100x oil immersion objective on a Nikon epifluorescence microscope using Metamorph deconvolution and imaging software.

EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be illustrative of the invention and not limiting of the reasonable scope thereof.

SCHEME 1



2-propyl-4H-3,1-benzoxazin-4-one (1-1)

A solution of anthranilic acid (3.40 g, 25.0 mmol) in butyric anhydride (10 mL) was heated at 150°C for 1 hOUR. The bath temperature was lowered to 90°C and the excess butyric anhydride was removed by distillation. The residue was distilled to provide 2-propyl-4H-3,1-benzoxazin-4-one (1-1) as a colorless liquid (bp 110-112°C/2 mm Hg), which solidified upon standing. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, 1H, J = 8 Hz, 1H), 7.80 (t, J = 7 Hz, 1H), 7.57 (d, J = 8 Hz, 1H), 7.50 (t, J = 7 Hz, 1H), 2.68 (t, J = 7 HZ, 2H), 1.87 (m, 2H), 1.05 (t, J = 7 Hz, 3H).

3-benzyl-2-propylquinazolin-4(3H)-one (1-2)

A solution of 2-propyl-4H-3,1-benzoxazin-4-one (1-1, 2.84 g, 15.0 mmol, 1 equiv.) and benzylamine(1.77g, 16.5 mmol, 1.10 equiv.) in chloroform (10 mL) was heated at reflux for 4 hours. The reaction mixture was concentrated and the residue was heated in a mixture of NaOH (60 mg, 1.5 mmol, 0.1 equiv.) in ethylene glycol (10 mL) at 135°C for 5 hours. The reaction mixture was cooled and diluted with water. The pH of the resulting mixture was adjusted to 7 by the addition of 6 N HCl. The insoluble solid was collected by filtration and recrystallized from acetone/ water to give 3-benzyl-2-propylquinazolin-4(3H)-one (1-2) as cream-colored crystals. ^{1}H NMR (500 MHz,$CDCl_3$) δ 8.31 (d, J = 8 Hz, 1H), 7.74 (t, J = 7 Hz, 1H),7.66 (d, J = 8 Hz, 1H), 7.46 (t, J = 8 Hz, 1H), 7.32 (m, 2H), 7.26 (m, 1H), 7.18 (d, J = 7 Hz, 2H), 2.72 (t, J = 7 Hz, 2 H), 1.80 (m, 2 H), 0.99 (t, J = 7 Hz, 3 H).

3-benzyl-2-(1-bromopropyl)quinazolin-4(3H)-one (1-3)

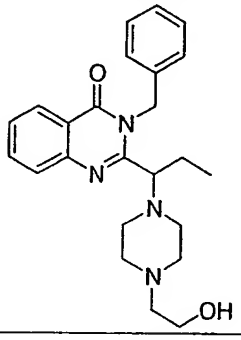
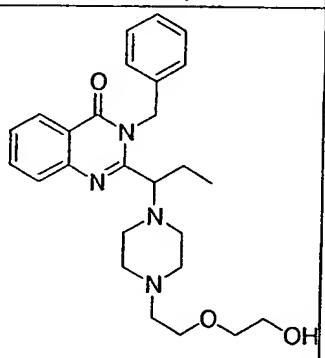
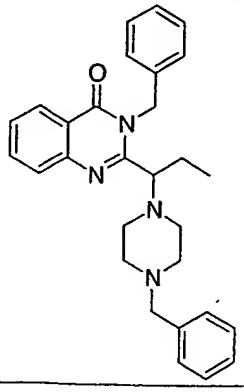
Bromine (1.9 g, 12 mmol, 1.2 equiv.) was added dropwise to a stirred solution of 3-benzyl-2-propylquinazolin-4(3H)-one (1-2, 2.78 g, 10.0 mmol, 1 equiv.) and sodium acetate(0.98 g, 12 mmol, 1.2 equiv.) in acetic acid (10 mL). The reaction was warmed at 45°C for 2 hours and then poured into water (300 mL). The resulting mixture was stirred for 2 hours and the solid collected by filtration to provide 3-benzyl-2(1-bromopropyl)quinazolin-4(3H)-one (1-3) as an off-white solid. 1H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, J = 7 Hz, 1H), 7.64 (m, 2H), 7.53 (t, J = 7 Hz, 1H), 7.33 (m, 2H), 7.28 (m, 1H), 7.15 (d, J = 7Hz, 2H), 6.22 (d, J = 16 Hz, 1H), 4.95 (d, J = 16 Hz, 1H), 4.64 (t, J = 7 Hz, 1H), 2.48 (m, 1H), 2.25 (m, 1H), 0.77 (t, J = 7 Hz, 3H).

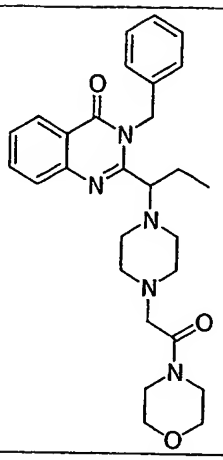
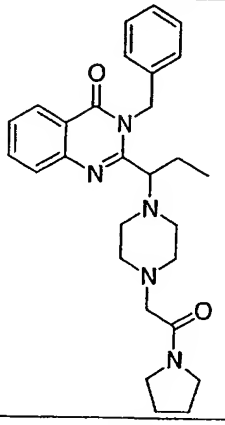
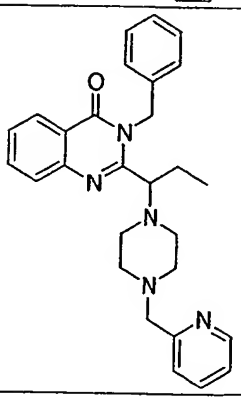
3-benzyl-2-[1-(4-methylpiperazin-1-yl)propyl]quinazolin-4(3H)-one (1-4)

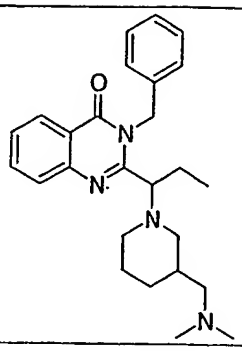
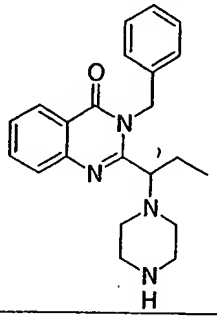
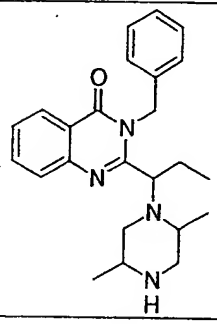
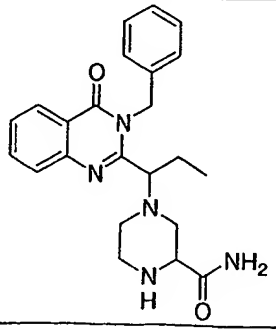
A solution of 3-benzyl-2-(1-bromopropyl)quinazolin-4(3H)-one (1-3, 36 mg, 0.1 mmol, 1 equiv.), N,N-diisopropylethylamine (13 mg, 0.1 mmol, 1.0 equiv.) and 4-methylpiperazine (10 mg, 0.1 mmol, 1.0 equiv.) in n-butanol (3 mL) was heated at 120°C for 18 hours. The product mixture was purified by reverse-phase liquid chromatography (H_2O/CH_3CN gradient w/ 0.1 % TFA present) to provide 3-benzyl-2-[1-(4-methylpiperazin-1-yl)propyl]quinazolin-4(3H)-one (1-4) as a TFA salt (pale yellow gum). ^{1}H NMR (500 MHz, CD_3OD) δ 8.28 (d, J = 8 Hz, 1H), 7.86 (t, J = 8 Hz, 1H), 7.75 (d, J = 8 Hz, 1H), 7.59 (t, J = 7 Hz, 1H), 7.35 (m, 2H), 7.29 (m, 1H), 7.16 (d, J= 7 Hz, 2 H), 5.78 (d, J = 17 Hz, 1H), 5.38 (d, J = 17 Hz, 1H), 3.84 (dd, J =

10, 4 Hz, 1H), 3.40 (m, 1H), 3.36 (m, 1H), 3.01 (m, 4H), 2.77 (s, 3H), 2.74 (m, 1H), 2.22 (m, 1H), 1.71 (m, 1H), 0.69 (t, J = 7 Hz, 3H).

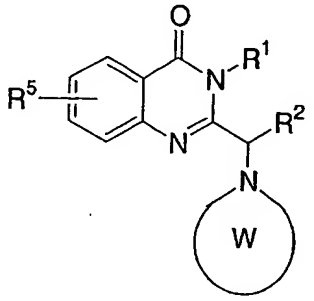
The following compounds were prepared by simple modifications of the above procedures. Compounds 1-11 to 1-15 were isolated as the TFA salt.

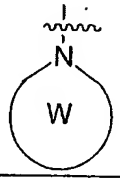
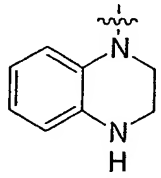
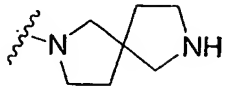
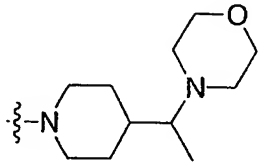
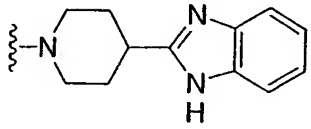
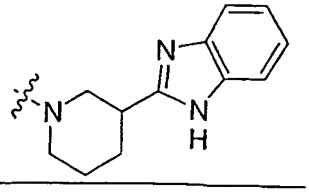
Compound	Name	Structure	LRMS *m/z* (M+H)
1-5	3-benzyl-2-{1-[4-(2-hydroxyethyl)piperazin-1-yl]propyl}quinazolin-4(3H)-one		407.1
1-6	3-benzyl-2-(1-{4-[2-(2-hydroxyethoxy)ethyl]-piperazin-1-yl}propyl) quinazolin-4(3H)-one		451.2
1-7	3-benzyl-2-[1-(4-benzylpiperazin-1-yl) propyl]quinazolin-4(3H)-one		453.2

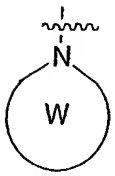
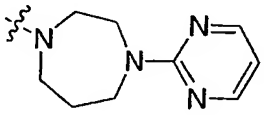
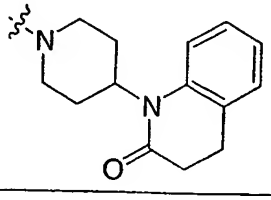
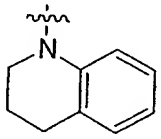
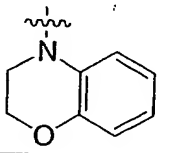
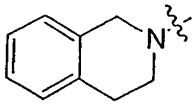
1-8	3-benzyl-2-{1-[4-(2-morpholin-4-yl-2-oxoethyl)piperazin-1-yl]propyl}quinazolin-4(3H)-one		490.3
1-10	3-benzyl-2-{1-[4-(2-oxo-2-pyrrolidin-1-ylethyl)piperazin-1-yl]propyl}quinazolin-4(3H)-one		474.2
1-11	3-benzyl-2-{1-[4-(pyridin-2-ylmethyl) piperazin-1-yl]propyl} quinazolin-4(3H)-one		454.2

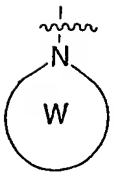
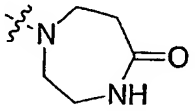
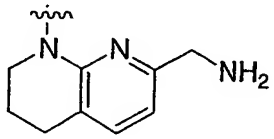
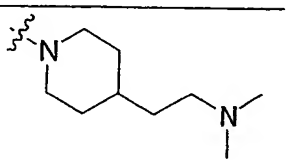
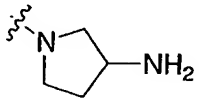
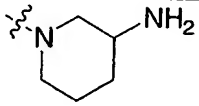
1-12	3-benzyl-2-(1-{3-[(dimethylamino)methyl]-piperidin-1-yl}propyl) quinazolin-4(3H)-one		419.2
1-13	3-benzyl-2-(1-piperazin-1-ylpropyl)quinazolin-4(3H)-one		363.1
1-14	3-benzyl-2-[1-(2,5-dimethylpiperazin-1-yl) propyl]quinazolin-4(3H)-one		391.2
1-15	4-[1-(3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl]piperazine-2-carboxamide		406.2

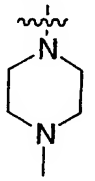
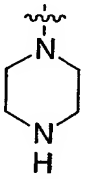
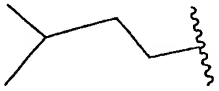
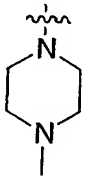
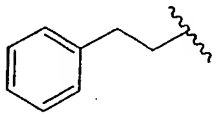
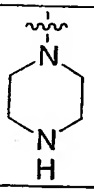
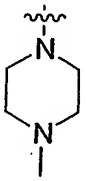
The compounds of the invention illustrated below can be prepared by the synthetic methods described hereinabove, but substituting the appropriate cyclic amine for the 4-methyl piperazine utilized in the example:

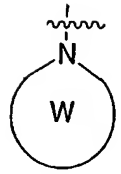
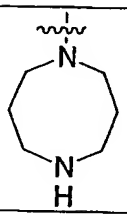
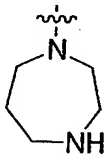
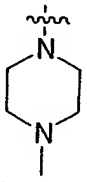
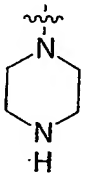
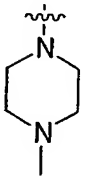


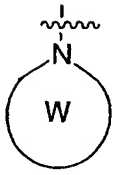
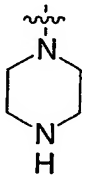
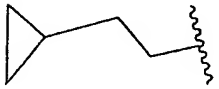
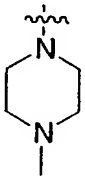
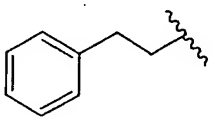
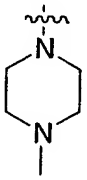
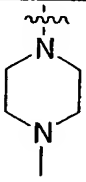
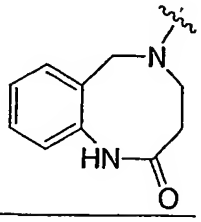
R^1	R^2	R^5	
Bn	Et	H	
Bn	Et	H	
Bn	Et	H	
Bn	Et	H	
Bn	Et	H	

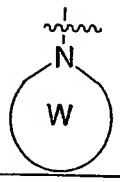
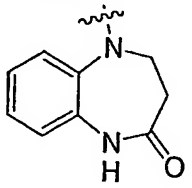
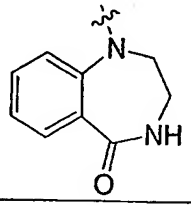
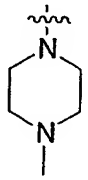
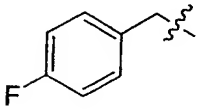
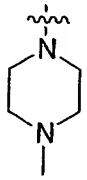
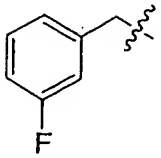
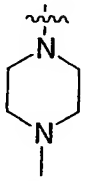
R^1	R^2	R^5	
Bn	Et	H	
Bn	Et	H	
Bn	Et	H	
Bn	Et	H	
Bn	Et	H	

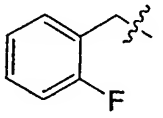
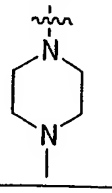
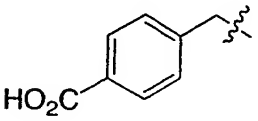
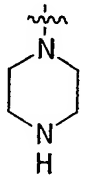
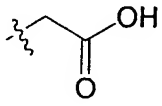
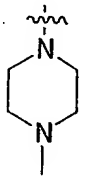
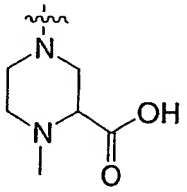
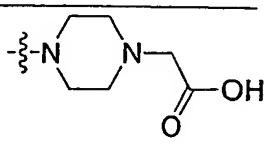
R^1	R^2	R^5	
Bn	Et	H	
Bn	Et	H	
Bn	Et	H	
Bn	Et	H	
Bn	Et	H	

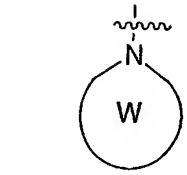
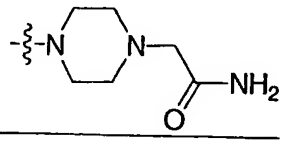
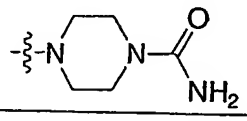
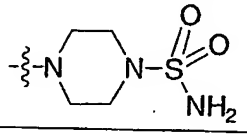
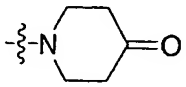
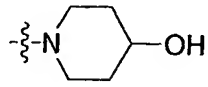
	R^1	R^2	R^5	W
	Bn	Et	6-F	
	Bn	Et	7-F	
		Et	H	
		Et	H	
		Et	H	

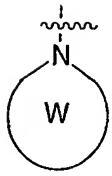
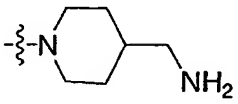
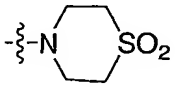
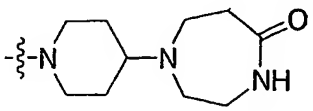
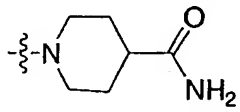
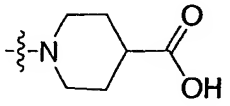
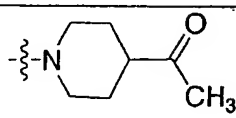
R^1	R^2	R^5	
Bn	Et	H	
Bn	Et	H	
Bn	Pr	H	
Bn	Et	5-F	
Bn	Et	6-Cl	

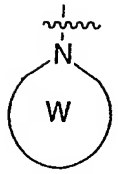
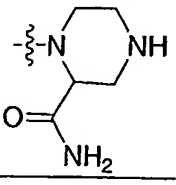
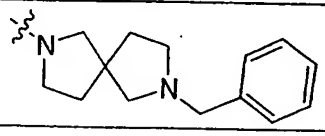
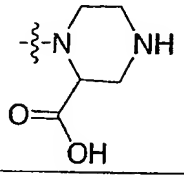
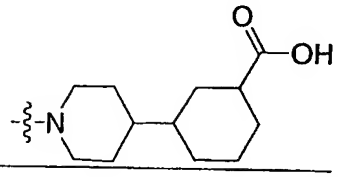
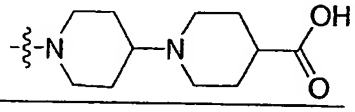
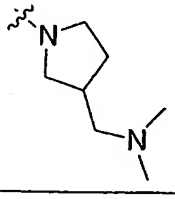
R^1	R^2	R^5	
Bn	Et	7-Cl	
	Et	H	
	Pr	H	
Bn	Me	H	
Bn	Et	H	

R^1	R^2	R^5	
Bn	Et	H	
Bn	Et	H	
Bn	Et	8-F	
	Et	H	
	Et	H	

R^1	R^2	R^5	W
	Et	H	
	Et	H	
Bn		H	
Bn	Et	H	
Bn	Et	H	

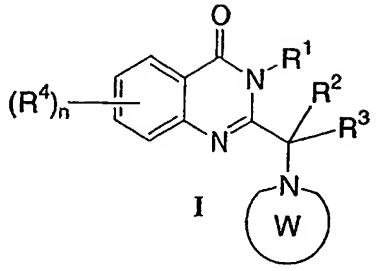
R^1	R^2	R^5	
Bn	Et	H	
Bn	Et	H	
Bn	Et	H	
Bn	Et	H	
Bn	Et	H	

R^1	R^2	R^5	
Bn	Et	H	
Bn	Et	H	
Bn	Et	H	
Bn	Et	H	
Bn	Et	H	
Bn	Et	H	

R^1	R^2	R^5	
Bn	Et	H	
Bn	Et	H	
Bn	Et	H	
Bn	Et	H	
Bn	Et	H	
Bn	Et	H	

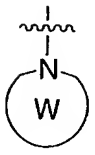
WHAT IS CLAIMED IS:

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein



is a 5-12 membered nitrogen-containing heterocycle, which is optionally substituted with from one to six R^5 groups and which optionally incoporates from one to two additional heteroatoms, selected from N, O and S in the heterocycle ring;

a is 0 or 1;
b is 0 or 1;
m is 0, 1, or 2;
n is 0 to 4;

R^1 is selected from:

1) H,
2) C_1-C_{10} alkyl,
3) aryl,
4) C_2-C_{10} alkenyl,
5) C_2-C_{10} alkynyl,
6) C_1-C_6 perfluoroalkyl,
7) C_3-C_8 cycloalkyl, and
8) heterocyclyl,

said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R^5;

R^2 and R^3 are independently selected from:

1) H,
2) $(C=O)_aO_bC_1$-C_{10} alkyl,
3) $(C=O)_aO_b$aryl,
4) $(C=O)_aO_bC_2$-C_{10} alkenyl,
5) $(C=O)_aO_bC_2$-C_{10} alkynyl,
6) CO_2H,
7) C_1-C_6 perfluoroalkyl,
8) $(C=O)_aO_bC_3$-C_8 cycloalkyl,
9) $(C=O)_aO_b$heterocyclyl,
10) $SO_2NR^7R^8$, and
11) SO_2C_1-C_{10} alkyl,

said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R^5;

R^4 is independently selected from:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,
2) $(C=O)_aO_b$aryl,
3) $(C=O)_aO_bC_2$-C_{10} alkenyl,
4) $(C=O)_aO_bC_2$-C_{10} alkynyl,
5) CO_2H,
6) halo,
7) OH,
8) O_bC_1-C_6 perfluoroalkyl,
9) $(C=O)_aNR^7R^8$,
10) CN,
11) $(C=O)_aO_bC_3$-C_8 cycloalkyl,
12) $(C=O)_aO_b$heterocyclyl,
13) $SO_2NR^7R^8$, and
14) SO_2C_1-C_{10} alkyl,

said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R^5;

R^5 is:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,
2) $(C=O)_aO_b$aryl,
3) C_2-C_{10} alkenyl,
4) C_2-C_{10} alkynyl,
5) $(C=O)_aO_b$ heterocyclyl,
6) CO_2H,
7) halo,
8) CN,
9) OH,
10) O_bC_1-C_6 perfluoroalkyl,
11) $O_a(C=O)_bNR^7R^8$,
12) oxo,
13) CHO,
14) $(N=O)R^7R^8$, or
15) $(C=O)_aO_bC_3$-C_8 cycloalkyl,

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from R^6;

R^6 is selected from:

1) $(C=O)_rO_s(C_1$-$C_{10})$alkyl, wherein r and s are independently 0 or 1,
2) $O_r(C_1$-$C_3)$perfluoroalkyl, wherein r is 0 or 1,
3) $(C_0$-$C_6)$alkylene-$S(O)_mR^a$, wherein m is 0, 1, or 2,
4) oxo,
5) OH,
6) halo,
7) CN,
8) $(C=O)_rO_s(C_2$-$C_{10})$alkenyl,
9) $(C=O)_rO_s(C_2$-$C_{10})$alkynyl,
10) $(C=O)_rO_s(C_3$-$C_6)$cycloalkyl,
11) $(C=O)_rO_s(C_0$-$C_6)$alkylene-aryl,

12) $(C=O)_rO_s(C_0\text{-}C_6)$alkylene-heterocyclyl,
13) $(C=O)_rO_s(C_0\text{-}C_6)$alkylene-$N(R^b)_2$,
14) $C(O)R^a$,
15) $(C_0\text{-}C_6)$alkylene-CO_2R^a,
16) C(O)H,
17) $(C_0\text{-}C_6)$alkylene-CO_2H, and
18) $C(O)N(R^b)_2$,

said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from R^b, OH, $(C_1\text{-}C_6)$alkoxy, halogen, CO_2H, CN, $O(C=O)C_1\text{-}C_6$ alkyl, oxo, and $N(R^b)_2$;

R^7 and R^8 are independently selected from:

1) H,
2) $(C=O)O_bC_1\text{-}C_{10}$ alkyl,
3) $(C=O)O_bC_3\text{-}C_8$ cycloalkyl,
4) $(C=O)O_b$aryl,
5) $(C=O)O_b$heterocyclyl,
6) $C_1\text{-}C_{10}$ alkyl,
7) aryl,
8) $C_2\text{-}C_{10}$ alkenyl,
9) $C_2\text{-}C_{10}$ alkynyl,
10) heterocyclyl,
11) $C_3\text{-}C_8$ cycloalkyl,
12) SO_2R^a, and
13) $(C=O)NR^b{}_2$,

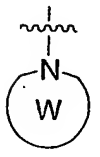
said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from R^6, or

R^7 and R^8 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocylcic or bicyclic heterocycle optionally substituted with one or more substituents selected from R^6;

R^a is $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, aryl, or heterocyclyl; and

R^b is H, $(C_1\text{-}C_6)$alkyl, aryl, heterocyclyl, $(C_3\text{-}C_6)$cycloalkyl, $(C{=}O)OC_1\text{-}C_6$ alkyl, $(C{=}O)C_1\text{-}C_6$ alkyl or $S(O)_2R^a$.

2. The compound of Claim 1, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein



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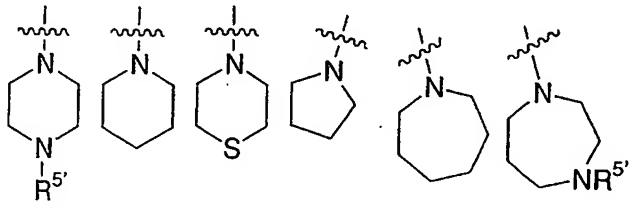


optionally substituted with from one to three R^5 groups:

$R^{5'}$ is:

1) H,
2) $C_1\text{-}C_{10}$ alkyl,
3) aryl,
4) $C_2\text{-}C_{10}$ alkenyl,
5) $C_2\text{-}C_{10}$ alkynyl,
6) heterocyclyl,
7) OH,
8) $C_1\text{-}C_6$ perfluoroalkyl,
9) $C_3\text{-}C_8$ cycloalkyl;

said alkyl, aryl, alkenyl, alkynyl and heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from R6..

3. The compound according to Claim 2 or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

a is 0 or 1;
b is 0 or 1;

m is 0, 1, or 2;
n is 0 to 4;

R^1 is selected from:

1) H,
2) C_1-C_{10} alkyl,
3) aryl,
4) C_3-C_8 cycloalkyl, and
5) heterocyclyl,

said alkyl, aryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R^5;

R^2 and R^3 are independently selected from:

1) H,
2) $(C=O)_aO_bC_1$-C_{10} alkyl,
3) $(C=O)_aO_b$aryl,
4) CO_2H,
5) C_1-C_6 perfluoroalkyl,
6) $(C=O)_aO_bC_3$-C_8 cycloalkyl, and
7) $(C=O)_aO_b$heterocyclyl,

said alkyl, aryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R^5;

R^4 is independently selected from:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,
2) $(C=O)_aO_b$aryl,
3) CO_2H,
4) halo,
5) OH,
6) O_bC_1-C_6 perfluoroalkyl,
7) $(C=O)_aNR^7R^8$,
8) CN,
9) $(C=O)_aO_b$heterocyclyl,
10) $SO_2NR^7R^8$, and

11) SO_2C_1-C_{10} alkyl,

said alkyl, aryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R^5;

R^5 is:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,
2) $(C=O)_aO_b$aryl,
3) C_2-C_{10} alkenyl,
4) C_2-C_{10} alkynyl,
5) $(C=O)_aO_b$ heterocyclyl,
6) CO_2H,
7) halo,
8) CN,
9) OH,
10) O_bC_1-C_6 perfluoroalkyl,
11) $O_a(C=O)_bNR^7R^8$,
12) oxo,
13) CHO,
14) $(N=O)R^7R^8$, or
15) $(C=O)_aO_bC_3$-C_8 cycloalkyl,

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from R^6;

R^5' is:

1) H,
2) C_1-C_{10} alkyl,
3) aryl,
4) C_2-C_{10} alkenyl,
5) C_2-C_{10} alkynyl,
6) heterocyclyl,
7) OH,
8) C_1-C_6 perfluoroalkyl,
9) C_3-C_8 cycloalkyl;

said alkyl, aryl, alkenyl, alkynyl and heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from R^6;

R^6 is selected from:

1) $(C=O)_rO_s(C_1\text{-}C_{10})$alkyl, wherein r and s are independently 0 or 1,
2) $O_r(C_1\text{-}C_3)$perfluoroalkyl, wherein r is 0 or 1,
3) oxo,
4) OH,
5) halo,
6) CN,
7) $(C_2\text{-}C_{10})$alkenyl,
8) $(C_2\text{-}C_{10})$alkynyl,
9) $(C=O)_rO_s(C_3\text{-}C_6)$cycloalkyl,
10) $(C=O)_rO_s(C_0\text{-}C_6)$alkylene-aryl,
11) $(C=O)_rO_s(C_0\text{-}C_6)$alkylene-heterocyclyl,
12) $(C=O)_rO_s(C_0\text{-}C_6)$alkylene-$N(R^b)_2$,
13) $C(O)R^a$,
14) $(C_0\text{-}C_6)$alkylene-CO_2R^a,
15) C(O)H,
16) $(C_0\text{-}C_6)$alkylene-CO_2H, and
17) $C(O)N(R^b)_2$,

said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from R^b, OH, $(C_1\text{-}C_6)$alkoxy, halogen, CO_2H, CN, $O(C=O)C_1\text{-}C_6$ alkyl, oxo, and $N(R^b)_2$;

R^7 and R^8 are independently selected from:

1) H,
2) $(C=O)O_bC_1\text{-}C_{10}$ alkyl,
3) $(C=O)O_bC_3\text{-}C_8$ cycloalkyl,
4) $(C=O)O_b$aryl,
5) $(C=O)O_b$heterocyclyl,
6) $C_1\text{-}C_{10}$ alkyl,
7) aryl,
8) $C_2\text{-}C_{10}$ alkenyl,

9) C_2-C_{10} alkynyl,
10) heterocyclyl,
11) C_3-C_8 cycloalkyl,
12) SO_2R^a, and
13) $(C=O)NR^b{}_2$,

said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from R^6, or

R^7 and R^8 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocylcic or bicyclic heterocycle optionally substituted with one or more substituents selected from R^6;

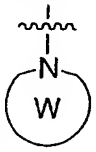
R^a is $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, aryl, or heterocyclyl; and

R^b is H, $(C_1$-$C_6)$alkyl, aryl, heterocyclyl, $(C_3$-$C_6)$cycloalkyl, $(C=O)OC_1$-C_6 alkyl, $(C=O)C_1$-C_6 alkyl or $S(O)_2R^a$.

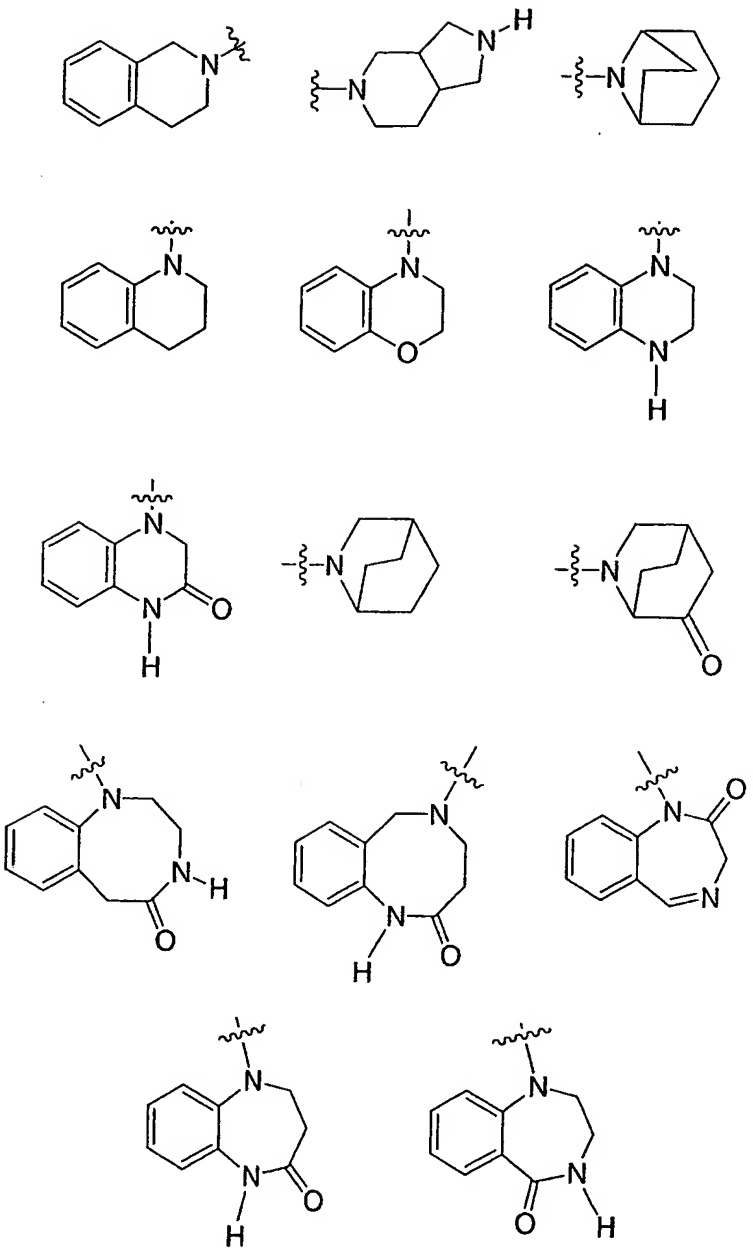
4. The compound according to Claim 3, or the pharmaceutically acceptable salt or stereoisomer thereof, wherein R^1 is selected from: H, $(C_1$-$C_6)$alkyl, aryl and benzyl.

5. The compound according to Claim 3, or the pharmaceutically acceptable salt or stereoisomer thereof, wherein R^1 is benzyl, optionally substituted with one to three substituents selected from R^5; R^2 is C_2-C_6-alkyl and R^3 is H.

6. The compound of Claim 1, or a pharmaceutically acceptable salt or stereoisomer thereof,



wherein is selected from:



optionally substituted with from one to three R^5 groups;

a is 0 or 1;

b is 0 or 1;

m is 0, 1, or 2;

n is 0 to 4;

R^1 is benzyl, optionally substituted with one to three substituents selected from R^5;

R^2 is C_2-C_6 alkyl;

R^3 is H;

R^4 is independently selected from:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,
2) $(C=O)_aO_b$aryl,
3) CO_2H,
4) halo,
5) OH,
6) O_bC_1-C_6 perfluoroalkyl,
7) $(C=O)_aNR^7R^8$,
8) CN,
9) $(C=O)_aO_b$heterocyclyl,
10) $SO_2NR^7R^8$, and
11) SO_2C_1-C_{10} alkyl,

said alkyl, aryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R^5;

R^5 is:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,
2) $(C=O)_aO_b$aryl,
3) C_2-C_{10} alkenyl,
4) C_2-C_{10} alkynyl,
5) $(C=O)_aO_b$ heterocyclyl,
6) CO_2H,
7) halo,
8) CN,
9) OH,

10) O_bC_1-C_6 perfluoroalkyl,
11) $O_a(C=O)_bNR^7R^8$,
12) oxo,
13) CHO,
14) $(N=O)R^7R^8$, or
15) $(C=O)_aO_bC_3$-C_8 cycloalkyl,

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from R^6;

R^6 is selected from:

1) $(C=O)_rO_s(C_1$-$C_{10})$alkyl, wherein r and s are independently 0 or 1,
2) $O_r(C_1$-$C_3)$perfluoroalkyl, wherein r is 0 or 1,
3) oxo,
4) OH,
5) halo,
6) CN,
7) $(C_2$-$C_{10})$alkenyl,
8) $(C_2$-$C_{10})$alkynyl,
9) $(C=O)_rO_s(C_3$-$C_6)$cycloalkyl,
10) $(C=O)_rO_s(C_0$-$C_6)$alkylene-aryl,
11) $(C=O)_rO_s(C_0$-$C_6)$alkylene-heterocyclyl,
12) $(C=O)_rO_s(C_0$-$C_6)$alkylene-$N(R^b)_2$,
13) $C(O)R^a$,
14) $(C_0$-$C_6)$alkylene-CO_2R^a,
15) C(O)H,
16) $(C_0$-$C_6)$alkylene-CO_2H, and
17) $C(O)N(R^b)_2$,

said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from R^b, OH, $(C_1$-$C_6)$alkoxy, halogen, CO_2H, CN, $O(C=O)C_1$-C_6 alkyl, oxo, and $N(R^b)_2$;

R^7 and R^8 are independently selected from:

1) H,
2) $(C=O)O_bC_1$-C_{10} alkyl,

3) $(C=O)O_bC_3$-C_8 cycloalkyl,
4) $(C=O)O_b$aryl,
5) $(C=O)O_b$heterocyclyl,
6) C_1-C_{10} alkyl,
7) aryl,
8) C_2-C_{10} alkenyl,
9) C_2-C_{10} alkynyl,
10) heterocyclyl,
11) C_3-C_8 cycloalkyl,
12) SO_2R^a, and
13) $(C=O)NR^b{}_2$,

said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from R^6, or

R^7 and R^8 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocylcic or bicyclic heterocycle optionally substituted with one or more substituents selected from R^6;

R^a is $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, aryl, or heterocyclyl; and

R^b is H, $(C_1$-$C_6)$alkyl, aryl, heterocyclyl, $(C_3$-$C_6)$cycloalkyl, $(C=O)OC_1$-C_6 alkyl,
$(C=O)C_1$-C_6 alkyl or $S(O)_2R^a$.

7. A compound selected from:

3-benzyl-2-[1-(4-methylpiperazin-1-yl)propyl]quinazolin-4(3H)-one;

3-benzyl-2-{1-[4-(2-hydroxyethyl)piperazin-1-yl]propyl}quinazolin-4(3H)-one;

3-benzyl-2-(1-{4-[2-(2-hydroxyethoxy)ethyl]-piperazin-1-yl}propyl)quinazolin-4(3H)-one;

3-benzyl-2-[1-(4-benzylpiperazin-1-yl)propyl]quinazolin-4(3H)-one;

3-benzyl-2-{1-[4-(2-morpholin-4-yl-2-oxoethyl)piperazin-1-yl]propyl}quinazolin-4(3H)-one;

3-benzyl-2-{1-[4-(2-oxo-2-pyrrolidin-1-ylethyl)piperazin-1-yl]propyl}quinazolin-4(3H)-one;

3-benzyl-2-{1-[4-(pyridin-2-ylmethyl)piperazin-1-yl]propyl}quinazolin-4(3H)-one;

3-benzyl-2-(1-{3-[(dimethylamino)methyl]-piperidin-1-yl}propyl)quinazolin-4(3H)-one;

3-benzyl-2-(1-piperazin-1-ylpropyl)quinazolin-4(3H)-one;

3-benzyl-2-[1-(2,5-dimethylpiperazin-1-yl)propyl]quinazolin-4(3H)-one;

4-[1-(3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl]piperazine-2-carboxamide;

or a pharmaceutically acceptable salt or stereoisomer thereof.

8. A compound according to Claim 7 selected from:

3-benzyl-2-[1-(4-methylpiperazin-1-yl)propyl]quinazolin-4(3H)-one;

3-benzyl-2-{1-[4-(2-hydroxyethyl)piperazin-1-yl]propyl}quinazolin-4(3H)-one;

3-benzyl-2-[1-(4-benzylpiperazin-1-yl)propyl]quinazolin-4(3H)-one;

3-benzyl-2-{1-[4-(2-morpholin-4-yl-2-oxoethyl)piperazin-1-yl]propyl}quinazolin-4(3H)-one;

3-benzyl-2-(1-{3-[(dimethylamino)methyl]-piperidin-1-yl}propyl)quinazolin-4(3H)-one;

or a pharmaceutically acceptable salt or stereoisomer thereof.

9. A TFA salt of a compound selected from:

3-benzyl-2-[1-(4-methylpiperazin-1-yl)propyl]quinazolin-4(3H)-one;

3-benzyl-2-{1-[4-(pyridin-2-ylmethyl)piperazin-1-yl]propyl}quinazolin-4(3H)-one;

3-benzyl-2-(1-{3-[(dimethylamino)methyl]-piperidin-1-yl}propyl)quinazolin-4(3H)-one;

3-benzyl-2-(1-piperazin-1-ylpropyl)quinazolin-4(3H)-one;

3-benzyl-2-[1-(2,5-dimethylpiperazin-1-yl)propyl]quinazolin-4(3H)-one; and

4-[1-(3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)propyl]piperazine-2-carboxamide

or a stereoisomer thereof.

10. A pharmaceutical composition that is comprised of a compound in accordance with Claim 1 and a pharmaceutically acceptable carrier.

11. A method of treating or preventing cancer in a mammal in need of such treatment that is comprised of administering to said mammal a therapeutically effective amount of a compound of Claim 1.

12. A method of treating cancer or preventing cancer in accordance with Claim 11 wherein the cancer is selected from cancers of the brain, genitourinary tract, lymphatic system, stomach, larynx and lung.

13. A method of treating or preventing cancer in accordance with Claim 11 wherein the cancer is selected from histiocytic lymphoma, lung adenocarcinoma, small cell lung cancers, pancreatic cancer, gioblastomas and breast carcinoma.

14. A process for making a pharmaceutical composition which comprises combining a compound of Claim 1 with a pharmaceutically acceptable carrier.

15. The composition of Claim 10 further comprising a second compound selected from:

1) an estrogen receptor modulator,
2) an androgen receptor modulator,
3) retinoid receptor modulator,
4) a cytotoxic agent,
5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,
8) an HIV protease inhibitor,
9) a reverse transcriptase inhibitor,
10) an angiogenesis inhibitor, and
11) a PPAR-γ agonist, and
12) PPAR-δ agonists.

16. The composition of Claim 15, wherein the second compound is an angiogenesis inhibitor selected from the group consisting of a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP inhibitor, an integrin blocker, interferon-α, interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-(chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, and an antibody to VEGF.

17. The composition of Claim 15, wherein the second compound is an estrogen receptor modulator selected from tamoxifen and raloxifene.

18. A method of treating cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 in combination with radiation therapy.

19. A method of treating or preventing cancer that comprises administering a therapeutically effective amount of a compound of Claim 1 in combination with a compound selected from:

1) an estrogen receptor modulator,
2) an androgen receptor modulator,
3) retinoid receptor modulator,
4) a cytotoxic agent,
5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,
8) an HIV protease inhibitor,
9) a reverse transcriptase inhibitor,
10) an angiogenesis inhibitor,
11) an inhibitor of inherent multidrug resistance,
12) an anti-emetic agent,
13) an agent useful in the treatment of anemia,
14) agent useful in the treatment of neutropenia, and
15) an immunologic-enhancing drug.

20. A method of treating cancer that comprises administering a therapeutically effective amount of a compound of Claim 1 in combination with radiation therapy and a compound selected from:

1) an estrogen receptor modulator,
2) an androgen receptor modulator,
3) retinoid receptor modulator,
4) a cytotoxic agent,
5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,
8) an HIV protease inhibitor,
9) a reverse transcriptase inhibitor,
10) an angiogenesis inhibitor,
11) an inhibitor of inherent multidrug resistance,
12) an anti-emetic agent,

13) an agent useful in the treatment of anemia,
14) agent useful in the treatment of neutropenia, and
15) an immunologic-enhancing drug.

21. A method of treating or preventing cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 and paclitaxel or trastuzumab.

22. A method of treating or preventing cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 and a GPIIb/IIIa antagonist.

23. The method of Claim 22 wherein the GPIIb/IIIa antagonist is tirofiban.

24. A method of treating or preventing cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 in combination with a COX-2 inhibitor.

25. A method of modulating mitotic spindle formation which comprises administering a therapeutically effective amount of a compound of Claim 1.

26. A method of inhibiting the mitotic kinesin KSP which comprises administering a therapeutically effective amount of a compound of Claim 1.

SEQUENCE LISTING

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Fraley, Mark E.
Hoffman, William F.

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